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COCCIDIOIDOMYCOSIS*

The Hazard Involved in Diagnostic Procedures, with Report of a Case

JOSEPH M. LOONEY, M.D.,† AND TOBIAS STEIN, M.D.‡

WEST ROXBURY, MASSACHUSETTS, AND MONTGOMERY, ALABAMA

THE health problem caused by the return of servicemen, who may act as carriers of diseases contracted overseas, is well known and needs no further elaboration. However, another health hazard, which has not received sufficient attention, has also arisen because of the dispersion of diseases not usually found in a given region. Such a disease, relatively rare in New England, is coccidioidomycosis. It has brought with it a serious hazard, which affects primarily the workers in the hospital laboratories who handle pathogenic material. Because of unfamiliarity with the disease, even well trained technicians may handle pathogenic cultures from these patients without being fully aware of the precautions required to prevent infection.

This paper is presented to call attention to the dangers involved in making a laboratory diagnosis of the presence of *Coccidioides immitis* in suspected material, and to describe a case of infection acquired by a technician.

A survey of the literature shows that 8 such cases of coccidioidomycosis, which were proved by the isolation and identification of the organism, have been reported. One of these cases resulted fatally. In addition to these cases, in which there were clinical manifestations of the disease, 25 cases of infection as shown by positive coccidioidin skin tests were also due to handling of cultures of the organism in laboratories. To this number 3 cases among our laboratory personnel who gave positive reactions to 1:100 coccidioidin antigen are added.

In 1928 Tomlinson and Bancroft[1-3] reported the first case in a twenty-six-year-old medical student who handled cultures of *C. immitis* in the laboratories of the medical schools of the Universities of Pennsylvania and Nebraska. His infection started as a pulmonary infection and after two weeks became generalized, with an abscess of the plantar surface of the left foot, from which C. *immitis* was isolated. The patient was treated with antimony and potassium tartrate and x-rays. The abscess healed. The patient remained apparently well for four years and then had a recurrence of the lesion in the foot, which was again treated as before, with healing. The patient has been well for fifteen years.

Dickson and Gifford[4] report the case of another twenty-six-year-old medical student who opened a Petri dish containing a culture several months old. A fine cloud of brownish dust arose when the dish was opened. After eight days he became ill with malaise and pleuritic pains in the chest. In the next three weeks he had constant headache, backache and aching legs, and lost 15 pounds in weight. A week later numerous red, painful nodules on both shins developed. These subsided in about eight days but reappeared after two months. Smith[5] reported that in his department 3 laboratory infections were found in which the fungus was isolated and that in 15 others a positive coccidioidin reaction was obtained. He does not give any further history, so that the infections may be assumed to have been mild.

Bush[6] reports the case of a medical technician who accidentally dropped a cotton wad used to plug a container in which fungi were being cultured. A cloud of dust arose from the cotton plug. Two weeks later the patient noted the first symptoms of malaise and weakness. This was followed on the next day with severe headache, backache and tenderness of the neck and ankles. There was an unproductive cough. X-ray films showed an area of density in the right lower lobe. The patient ran a fever in the afternoons, the temperature ranging from 101 to 104°F. Several erythema-nodosum lesions developed on the legs. Repeated x-ray films demonstrated an increase in the size of the lymph nodes of the right hilus that regressed in about two weeks. The sputum showed endosporulating spherules, and the coccidioidin skin test was strongly positive in 1:1000 dilution. The sedimentation rate was elevated to 24 mm. per hour, and an

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†Director, Clinical Laboratories, Veterans Administration Hospital, West Roxbury, Massachusetts.

‡Assistant professor of medicine, Alabama Medical College; chief, Medical Service, Veterans Administration Hospital, Montgomery, Alabama.

eosinophil count of 9 per cent was noted. The patient had symptoms of weakness, headache and backache for seven months. Smith and Harrell[7] recently reported a fatal case and 5 subclinical infections following the accidental contamination of the outside of some flasks with liquid cultures of *C. immitis*. The fatal case developed in a seventy-four-year-old Negro dishwasher in the Bacteriological Laboratory of Duke University School of Medicine. The skin test to coccidioidin never became definitely positive, but the complement-fixation test gave partial fixation in a 1:32 dilution. The organism was recovered from the sputum, and a month after the patient first became ill a generalized lymph-node enlargement developed. One lymph node was removed, and definite spherules containing endospores, characteristic of *C. immitis*, were found on section. The patient ran a spiking temperature for four months, when marked stiffness of the spine and generalized hyperalgesia of the skin developed. These symptoms gradually disappeared after a week, but he complained of a dull constant headache and stiffness of the neck. He gradually became comatose and died on the one hundred and seventieth day of his illness. The final diagnosis was generalized coccidioidomycosis with terminal meningitis.

Nabarro[8] reported a case occurring in a research chemist who was preparing extracts of the fungus for skin testing during which she wore a gauze mask. Two weeks later she complained of malaise and moderately severe pains in the right side of the chest. In twelve days she gave a positive skin test. On the following day her elbow was swollen and painful, and reddened nodules appeared on her shins. A dry nonproductive cough developed. On physical examination the chest showed impairment of resonance at both bases, with a few dry rales at the right apex and mid-zone. The erythema nodosum was fading. A sputum culture on Sabouraud's medium gave no growth, but guinea-pig inoculation was positive for *C. immitis*. Chest x-ray films, on admission, showed small irregular patches of consolidation, which gradually cleared after four months.

Of the 25 cases of subclinical infection, the greater number occurred in Smith's[5] laboratory. He reports 15 positive reactors in his laboratory, and in a personal communication he mentions 3 others in the same building but on different floors. Smith and Harrell[7] describe positive reactions among 4 laboratory technicians and 2 Negro workers in the cleaning room. Willett and Weiss[9] report a positive reaction in a member of their laboratory force.

In the following case the patient contracted the infection while examining a culture, taken from a patient in the hospital, which gave a typical growth on Sabouraud's medium.

Case Report

A 28-year-old Negro hospital laboratory technician was admitted to the Veterans Administration Hospital, West Roxbury, Massachusetts, on May 18, 1948, because of chest pain of 5 days' duration. He had been perfectly well until 5 days before entry, at which time, while at work, he had noted the onset of severe stabbing pain in the right side of the chest aggravated by breathing or motion. On the following day this had disappeared, but a similar pleuritic pain in the left side of the chest below the nipple developed. A temperature of 100.2°F. was recorded, accompanied by malaise but no chill. His general physical condition and a chest x-ray film taken at this time were entirely normal. He stayed home from work for the next 3 days but continued to run a temperature up to 102°F., with recurrent pleuritic pain in both sides of the chest, despite sulfadiazine in adequate doses and 300,000 units of penicillin parenterally on the night prior to admission to the hospital.

The past history revealed that he had had a gonorrheal infection in 1942, for which he had been treated with sulfadiazine with no sequelae. His mother had died of a tumor at the age of 44. The family history was otherwise irrelevant. He had been born and raised in Corpus Christi, Texas, and at the age of 18 had gone to school in Austin, Texas, where he had spent the next 4 years. During his military service he had been in various camps in Louisiana and in New England, but he had never been in the San Joaquin Valley or any of the other areas known to be endemic for coccidioidomycosis. He had been employed in the laboratory at the Veterans Administration Hospital, West Roxbury, Massachusetts, from September, 1946, until admission. After the diagnosis had been established he recalled that about 2 or 3 weeks prior to the onset of his symptoms he had spent about 30 to 45 minutes studying some old cultures of a fungous growth, which later was definitely identified as *C. immitis*. In examining these cultures he had removed the top of the Petri dish and had studied the gross specimens, at close range, with a magnifying lens, in addition to making smears for microscopical examination.

Physical examination revealed a well developed, well nourished man who did not appear acutely or chronically ill. He complained of pain in the left side of the chest associated with occasional cough. There were some shotty lymph nodes, bilaterally, in the cervical region and a few enlarged nodes in both axillas. The chest was normal except for a few medium, moist rales in the lower left anterior axillary line heard only after cough. The heart was normal, and the rest of the physical examination was essentially negative.

The temperature was 100°F., the pulse 72, and the respirations 18. The blood pressure was 120/70.

Urinalysis demonstrated a pH reaction of 6.5, a specific gravity of 1.025 and negative tests for albumin and sugar; microscopical examination of the sediment was negative. The white-cell count was 12,000, with 61 per cent neutrophils, 37 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. A smear showed the sputum to be loaded with streptococci and to contain a few gram-negative cocci. Preliminary reports on the sputum culture disclosed almost a pure culture of alpha-hemolytic streptococcus as well as a few colonies of *Staphylococcus albus*. Repeated sputum examinations, including many concentrated specimens, were found to be negative for acid-fast organisms. Repeated stools were reported negative for ova, blood and parasites. Heterophil-antibody agglutinations were positive in a dilution of 1:56, agglutinins for *Eberthella typhosa* (Type O) were present in 1:160, Type H in 1:320, paratyphoid organisms in 1:40, and *Salmonella schottmuelleri* in 1:80; agglutinations for *Brucella abortus* and Weil-Felix bacillus were negative. Bone-marrow smears showed hyperplasia, probably in response to infection. Repeated blood cultures were negative.

X-ray examination of the chest revealed moderate elevation of the left leaf of the diaphragm and an area of slight hazy infiltration throughout the entire left-lung field. There was also a patch of infiltration in the region of the right apex and slight haziness surrounding the right hilus. Another such area was seen overlying the left third rib anteriorly. It was believed that these findings were probably due to the presence of an atypical pneumonia. The x-ray findings are shown in Figure 1.

The patient continued to run a septic course with daily spikes in temperature from 102 up to 103.6°F. for the next 2 months. During this time there was a gradually increased leukocytosis and eosinophilia. On June 8 the white-cell count reached a maximum of 21,600, with 61 per cent neutrophils, 30 per cent lymphocytes, 2 per cent monocytes and 7 per cent eosinophils. The eosinophils gradually increased up to 16 per cent in the 3rd week. Follow-up x-ray films revealed very definite enlargement of the upper mediastinum and of the hilar lymph nodes, with a slight further increase in the infiltration in the parenchyma of the lung, especially the left lower lobe. The skin test showed a positive reaction to 1:100 coccidioidin and a negative reaction to *Trichinella spiralis* extract. The appetite remained good, but the patient continued to lose weight. He presented a positive skin reaction to first-strength purified protein derivative. Various diagnostic possibilities were considered, including tuberculosis, miliary in type, sarcoid, coccidioidomycosis, Loeffler's syndrome, various types of bacterial, rickettsial and virus diseases and lymphoma. A definite diagnosis was established on June 12, when *C. immitis* was identified from a sputum culture. This was confirmed by repeated identification of this organism from successive sputum cultures. On June 9 a course of penicillin, 100,000 units every 3 hours, was started and was continued for 9 days. This caused no appreciable change in the patient's clinical course. Further therapy consisted of complete bed rest with a high-calorie diet including protein supplements and supportive and symptomatic measures.

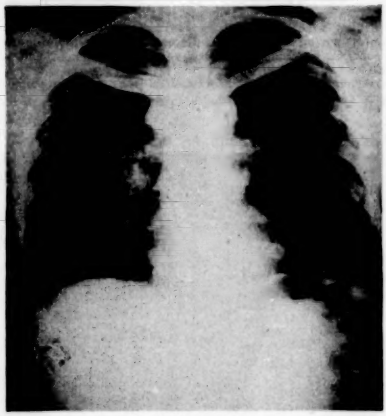

FIGURE 1. *X-Ray Film of the Chest, Showing Enlarged Mediastinal Lymph Nodes.*

The diagnosis of coccidioidomycosis was confirmed when specimens of blood sent to Dr. Charles E. Smith, at the Stanford University School of Medicine, were reported as showing a ++++ complement-fixation test in dilutions up to 1:64, and a + reaction in a dilution of 1:128. Precipitin tests with serial dilutions of the antigen were ++++ in a 1:10 dilution and +++ in a 1:40 dilution. The conclusion of Dr. Smith was as follows: "This confirms your diagnosis of severe coccidioidal infection in the range of dissemination."

During the 3rd month of hospitalization the patient continued to run a low-grade fever, the temperature rising to about 100°F. and occasionally a little higher, after which it dropped to normal, remaining so during the following 67 days of hospitalization. Repetitions of the complement-fixation tests were made by Dr. Charles E. Smith. The results are shown in Table 1. All precipitin tests, after the initial one, were entirely negative.

FIGURE 2. *Film of the Left Hand, Taken in November, 1948, Showing Involvement of the Second and Fourth Metacarpals.*

On August 16 it was noted that there was a small, firm nodular swelling in the lateral aspect of the left tibia about 2.5 cm. above the ankle. This was moderately tender to palpation; it appeared to be attached to the muscle tendon and moved with it. The node was approximately 1 cm. in diameter. There was no redness. This remained for the duration of the hospital stay but gradually decreased in size. No other nodules were noted. The course, though very slow, showed progressive improvement and during the last 2 months of hospital stay the patient's weight gradually increased from 154 pounds to 173 pounds at the time of discharge from the hospital. The sedimentation rate remained elevated at 35-38 mm. per hour throughout the course of the disease and even on the day of discharge was reported as 28 mm. per hour. However, in accordance with Dr. Smith's recommendation, it was believed that the patient could probably do as well at home as in the hospital, and he was discharged on October 17, after 157 days of hospitalization. He was advised to conduct his life on a schedule of spending 16 hours a day in bed and to return to the hospital for frequent periodic checkups and physical, x-ray and blood studies.

TABLE 1. *Laboratory Data.*

Date	Complement-Fixation Test							Precipitin Test		
	1:2	1:4	1:8	1:16	1:32	1:64	1:128	undiluted	1:10	1:40
6-27-48 ...	++++	++++	++++	++++	++++	++++	±	++++	++++	++++
9-23-48 ...	++++	++++	++++	++++	+++	+	0	0	0	0
11-24-48 ..	++++	++++	++++	+++	++	±	0	0	0	0
2-7-49	++++	++++	++++	+++	+	0	0	0	0	0
5-23-49 ...	++++	++++	++++	++++	+	0	0	0	0	0

He was readmitted to the hospital on November 17, with a temperature of 101°F. and a painful swelling of the left hand. He stated that he had noted some pain in the left hand and right foot before discharge but had paid little attention to it. He had no cough or chest pain at this time.

FIGURE 3. *Film of the Right Foot, Taken in November, 1948, Showing Involvement of the Fourth Metatarsals.*

The temperature showed daily elevations every afternoon, spiking to 104.2°F. On November 18 an x-ray film of the left hand demonstrated involvement of the distal half of the shaft of the fourth metacarpal. At that time no involvement of the bones of the right foot was found. A week later definite

FIGURE 4. *Film of the Left Hand, Taken in May, 1949, Showing Progression to the Base of the Fourth Metacarpal.*

changes were seen in the fourth metatarsal of this foot. The destructive process extended to involve the fifth metatarsal and then also the joint surface of the fourth toe. The swelling and tenderness of the hand increased, and further x-ray examinations showed involvement of the second metacarpal (Fig. 2 and 3). The dorsal surface of the right foot, in the region of the head of the fourth metatarsal, became fluctuant about December 20 and ruptured spontaneously 10 days later, discharging sanguinopurulent material on which a smear demonstrated numerous spherules of *C. immitis*. The lesion on the foot was incised widely under local anesthesia, with marked relief in the pain and tenderness.

During the next 3 weeks the bony changes in the left hand progressed, and the soft tissue on the dorsum of the hand became swollen and fluctuant in the two areas above the infected bones. The abscess cavities were aspirated several times, but since no definite improvement was obtained, the abscesses were finally incised and drained on January 20, 1949.

Attempts at therapy consisted of large doses of penicillin and caronamide; 800,000 units of penicillin and 2 gm. of

FIGURE 5. *Film of the Right Foot, Taken in May, 1949, Showing Destruction of the Joint Surface of the Fourth Metatarsal.*

caronamide were given every 3 hours for 3 weeks. During this period the urine specimens showed repeated ++ to +++ tests for albumin, with many red and white blood cells in the sediment. This was followed by a 5 weeks' course of 6 gm. of Promizole daily. In February he received seven x-ray treatments to the left hand. Each treatment consisted of 50 r through 2.3 cm. of copper filtrations for a total of 350 r. The patient believed that this treatment was beneficial. In March he was given aureomycin, 0.5 gm. every 4 hours for 1 week, but because of nausea, vomiting and malaise, the dose was reduced to 0.5 gm. every 6 hours. Two months later he was given Chloromycetin, 5 gm. on the 1st day and 2 gm. daily for 14 days.

The patient's general condition continued to improve, and he felt well. X-ray films of the chest showed a disappearance of the lung changes and a return of the mediastinal lymph nodes to a normal size.

The wounds of the hand and foot gradually closed but still showed a slight discharge. Despite this improvement the bony changes progressed, and x-ray studies revealed a new area of involvement at the base of the fourth left metacarpal. In April and in May the head of the fourth metatarsal of the right foot showed practically complete dissolution of the joint surface (Fig. 4 and 5).

Discussion

The evidence that this infection was contracted in the laboratory is conclusive. In the first place, the patient had never been in an area where coccidioidal infections are endemic. Secondly, the strongly positive precipitin tests are indicative of recent infection. It is to be noted that only the initial serum gave a positive precipitin test, all subsequent tests being negative. Thirdly, the dissemination that occurred in this patient indicated the recent origin of the infection. Smith[10] states "With very few exceptions, in a few weeks or months after the infection has been acquired, dissemination, if it is going to occur, will have developed."

Finally, the sudden onset with severe chest pain and spiking temperature is typical of the acute respiratory form of the initial infection.

The diagnosis in the early stages of the disease is difficult to make. The roentgenographic changes in the lung are not specific. The lung lesions are, as a rule, indistinguishable from bronchopneumonia or tuberculosis. Rapid enlargement of the hilar lymph nodes is frequently seen, as well demonstrated in this case (Fig. 1).

In the later stages if cavitation occurs the presence of thin-walled cavities with a minimal amount of tissue reaction surrounding them should make one suspicious of a coccidioidal infection. Two of the patients in this hospital showed such cavitation and were treated by lobectomy. It was while the culture from one of these patients was being examined that the technician became infected.

An increase in eosinophils is found in most cases, with counts ranging from 5 to 20 per cent. In a third of the cases a moderate leukocytosis may occur, the white-cell count ranging from 12,000 to 20,000. The patient discussed above showed both these signs, with an eosinophil count of 16 per cent and a white-cell count of 21,600.

The erythrocyte sedimentation rate is invariably increased, the rate ranging up to 40 mm. per hour by the Wintrobe method. This was also seen in our patient, whose rate increased to 40 mm. per hour and was still above 20 mm. before his last period of leave.

The complement-fixation test is an invaluable aid, and the presence of a high titer, 1:32 or more, in a patient's serum is indicative of dissemination. The persistence of the elevation of the titer is evidence of continued activity, whereas a fall in the titer parallels subsidence of the infection. The values found in our patient (Table 1) indicated some improvement but were still too high to rule out the possibility of further dissemination.

The skin test with coccidioidin is most helpful but must be interpreted with care. A positive test in a person with a previously negative reaction is prima-facie evidence of infection. Since the time necessary for the development of a positive test may be about four weeks, all suspects who give an initial negative reaction should be retested after four to six weeks.

A negative skin test does not rule out the possibility of infection. One of the patients with cavitation mentioned above gave repeated negative reactions. Furthermore, in the stage of dissemination the test may be negative in certain cases, and this is a poor prognostic sign.

A definite early diagnosis can only be made by recovery of the organism from sputum or from biopsy material. The finding of typical spherules, with heavy double refractile walls, containing endospores, is diagnostic. The mature spherules range from 10 to 60 microns in diameter but at times may attain a size three times as large.

Cultures grow well on Sabouraud's agar and have a typical appearance (Fig. 6). However, a definite diagnosis cannot be made without examination of the older growths for chlamydospores.

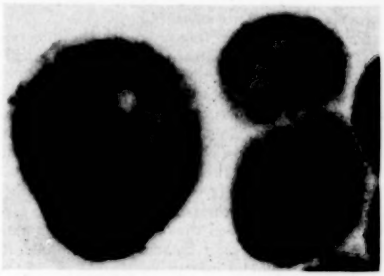

Figure 6. *Culture on Sabouraud's Agar.*

This is an extremely hazardous procedure and should be absolutely forbidden. The danger is not only that the person making the examination may be infected but also that others who may be long distances from the spot may also be infected.

Dr. Charles E. Smith, who has had a greater experience with this organism than any other investigator, identified the fungus as *C. immitis*. He stated, in a personal communication: "We have just had some of our neighbors in our building infected, and so are not handling cultures on solid mediums any longer either, and thus shall not be able to send you final identification." These infections occurred in the second and third floors of a building in which Smith's laboratory occupied the first floor. It is with good reason, therefore, that he states, "Actually, *C. immitis* in the laboratory is one of the most hazardous agents with which one can deal."

At present the consensus of the investigators in this field is that the disease is not contagious. Person-to-person or animal-to-person transfer of infection does not take place. However, Rosenthal and Routien[11] claim that person-to-person spread of the disease is possible.

As a result of the infection described above, it is now forbidden for anyone in our laboratory to open a culture showing any suspicious growth. The culture plates are sealed and are not opened until they have been autoclaved.

We also found that 3 of our technicians, who have never been in endemic areas, gave positive skin reactions. Of these, 2 were Negroes, and the other was of Italian descent. Thus, among 20 persons working in the laboratory, 1 disseminated and 3 subclinical infections occurred. Three of the 4 infections occurred in Negroes, and this is in agreement with previous experience[2, 5, 6, 9, 10] that colored races are more susceptible and that dissemination is ten times as prevalent among colored males as among white ones.

There is no specific treatment for the infection. Our patient received massive doses of penicillin and also aureomycin, Chloromycetin and Promizole, without any appreciable effect. The patient believed that the hand abscesses, which were irradiated, showed more rapid improvement than those of the foot, which was not. Tomlinson and Bancroft[1-3] reported that x-ray therapy and potassium antimony tartrate were beneficial in a patient with involvement of the bones of the foot.

It is generally agreed that rest and symptomatic treatment are the only means now available for handling coccidioidal infections.

The economic loss involved by the contracting of an infection of *C. immitis* is considerable. Our patient has been confined to a hospital for fourteen months, except for short periods during which he has been allowed home on leave. He still has some drainage from the wounds on his hand and will not be able to return to work for several months.

Summary

A review of the literature of accidental infections caused by the handling of *Coccidioides immitis* cultures in the laboratory is presented. Eight cases of infection showing clinical manifestations, with 1 death, and 25 cases of infection as indicated by positive skin reactions are recorded in the literature.

A case of disseminated infection with *C. immitis* contracted during the handling of a culture in the laboratory is reported.

The danger of handling cultures of this organism in attempts to establish a diagnosis and the precautions to be taken are emphasized.

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COMPLETE PELVIC EVISCERATION IN THE MALE FOR COMPLICATED CARCINOMA OF THE RECTUM*

The Use of a Defunctionalized, Sterilized Loop of Colon for Ureterosigmoid Anastomosis

JESSE E. THOMPSON, M.D.,† AND CHESTER W. HOWE, M.D.‡

BOSTON

RADICAL excision of the pelvic viscera for advanced carcinoma of the female pelvic organs has been successfully accomplished by Brunschwig[1] and Parsons.[2] Brunschwig[3] has also recently reported a case of radical pelvic surgery in a man with advanced carcinoma of the sigmoid colon invading the urinary bladder.

Our experiences in dealing with complications following ureterointestinal anastomosis and pelvic evisceration have crystallized certain concepts regarding the preparation and management of such cases. Some of the complications commonly seen after this type of surgery are urinary-fecal fistulas, abdominal and perineal wound sepsis and chemical and electrolyte imbalance including the syndrome of acidosis and hyperchloremia. Thus, the avoidance of stricture, stasis and leakage and the elimination of sources of bacterial contamination are factors of major importance in the reconstruction of the urinary and alimentary tracts.

After a review of the literature it was our belief that the type of ureterointestinal anastomosis recently advocated by Cordonnier[4] would best avoid urinary stasis, inasmuch as it is a fundamental principle of intestinal surgery that a mucosa-to-mucosa anastomosis is of vital importance in avoiding scarring and stenosis. It has been repeatedly observed that the fecal discharge in urinary-fecal fistulas ceases promptly after proximal colostomy, and that the remaining urinary sinus then heals rapidly with simple catheter suction. Thus, preliminary proximal colostomy seems to be a reasonable precautionary measure against this complication. The next logical step is the utilization of the colostomy for instillation of properly chosen intestinal antiseptic agents in an attempt to reduce the bacterial flora as much as possible. In a recent case of resection of a carcinoma of the esophagus in which a segment of colon was used to bridge a gap between the esophagus and jejunum, the bowel was prepared through a colostomy and actual sterilization was accomplished. The same method of preparation of the bowel was employed in the case presented below. The details of the plan of bacteriologic study and selection of antibacterial agents have been reported elsewhere by Howe.[5]

We were afforded the opportunity of employing these principles in a patient with carcinoma of the rectum who, during a preoperative cystoscopic examination, sustained an inadvertent perforation of the prostatic urethra directly through the tumor mass into the rectum. It seemed clear that complete cure could be achieved only by radical removal of the rectum and the organs of the lower urinary tract.

CASE REPORT

W. O. (M.M.H. 337,318), a 64-year-old Russian man, entered the Massachusetts Memorial Hospitals on May 5, 1949, because of rectal bleeding. He had been well until 3 weeks before entry, when he first noted bloody stools. His bowel movements increased in number from 1 to 3 or 4 per day, and the caliber of the stools began to decrease. There was no pain, anorexia, fatigue or weight loss. The past history and a review of the systems were otherwise not remarkable.

Physical examination revealed a well developed and well nourished man. There was no lymphadenopathy. The heart was not enlarged. The lungs were clear. The abdomen was normal. Rectal examination revealed a large, friable, slightly movable mass on the anterior rectal wall at the level of the prostate gland, which appeared to be annular and to obstruct the lumen of the bowel. The lesion bled quite easily when palpated.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 150/90.

The hemoglobin was 9.8 gm. per 100 cc., and the hematocrit was 36 per cent. The white-cell count was 10,200, with a normal differential. The urine was normal. The nonprotein nitrogen was 32 mg. per 100 cc. The serum chloride was 96.9 milliequiv. per liter, the total plasma protein was 6.15 gm. per 100 cc. and the fasting blood sugar was 120 mg. per 100 cc.

Roentgenograms of the chest and lumbodorsal spine were normal except for osteoarthritis. An intravenous pyelogram showed early appearance of dye in both kidneys. The calyxes, pelvis and ureter on the right were normal. In the lower pole of the left kidney was a space-occupying lesion, 4 cm. in diameter, the exact nature of which could not be determined. The left ureter and bladder appeared normal. An electrocardiogram was normal. The rectal tumor was readily visualized and biopsied on sigmoidoscopic examination, and the pathological diagnosis was poorly differentiated adenocarcinoma of the rectum. The patient was given transfusions of whole blood until the hemoglobin was 12 gm. per 100 cc. and the hematocrit was 49 per cent. Oral administration of Sulfasuxidine in a dosage of 8 gm. daily was begun.

Retrograde pyelography was attempted on the 5th hospital day, but was abandoned when the cystoscope inadvertently perforated the prostatic urethra to emerge into the rectum through the center of the carcinomatous mass. A catheter was successfully placed in the bladder, and a right transverse loop colostomy was immediately performed. Daily doses of 600,000 units of crysticillin intramuscularly and 3 gm. of aureomycin orally were begun.

The colostomy was opened 3 days later, and irrigation of the distal colon was begun after cultures of the feces were taken for sensitivity studies. The fecal flora consisted of

*From the Surgical Service, Massachusetts Memorial Hospitals, and the Department of Surgery, Boston University School of Medicine.

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†Trainee, National Cancer Institute; resident in surgery, Massachusetts Memorial Hospitals.

‡Instructor in surgery, Boston University School of Medicine; associate visiting surgeon, Massachusetts Memorial Hospitals.

Staphylococcus albus, alpha-hemolytic streptococcus, alpha-hemolytic streptococcus (enterococcus type), *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), *Escherichia coli*, *Proteus vulgaris* and *Klebsiella pneumoniae* (*Bacillus mucosus capsulatus*). Serial dilution sensitivity tests showed that the mixed flora was sensitive to 5 gamma per cubic centimeter of aureomycin and 3.15 gamma per cubic centimeter of Chloromycetin. The irrigating solution consisted of 12 gm. of crushed Sulfasuxidine and 3 gm. of aureomycin in 1000 cc. of saline solution. This was instilled in 5 equally divided doses daily. Six days preoperatively Sulfathalidine was substituted for Sulfasuxidine because of its superiority in the presence of a colostomy, and the crysticillin was omitted. One

FIGURE 1. *Wounds and Colostomies on the Twentieth Postoperative Day.*

day before operation it was desired to use crysticillin prophylactically, so Sulfasuxidine was started again to avoid possible Sulfathalidine-penicillin antagonism.[6]

On May 26 laparotomy was performed. Exploration of the abdomen was negative for metastases. The rectal mass was low and apparently invaded the urethra and the base of the bladder. The space-occupying lesion in the left kidney was found to be a benign cyst. The mesosigmoid was divided, and the superior hemorrhoidal vessels were ligated and divided near their origins. The pelvic peritoneum was incised to expose the ureters and iliac vessels, and the incision was continued to circumscribe the bladder anteriorly. Both hypogastric arteries were ligated in continuity immediately distal to the superior gluteal branches. The bladder and prostate gland were dissected and freed. The rectum was dissected laterally and posteriorly, and the sigmoid was divided with a cautery. The distal stump was closed aseptically with the use of the Smithwick clamp.[7] A full-thickness segment of colon, approximately 1.0 cm. square, was excised from the site of division for bacteriologic study. The ureters were divided atraumatically at the pelvic brim, about 2.5 cm. of each ureter being mobilized. The sigmoid was brought to each ureter, and a mucosa-to-mucosa anastomosis in two layers, with interrupted No. 0000 chromic catgut sutures, was carried out, the left ureter being joined to the bowel proximal to the right one. Each anastomotic site was covered with a flap of peritoneum. No attempt was made to reperitonealize the pelvic floor. The colostomy was brought out through the wound, which was closed with catgut sutures to the peritoneum and a continuous, No. 32, stainless-steel-wire suture to the anterior fascia and rectus muscle. The pelvis, the abdominal cavity at the site of operation and the wound were irrigated with 100 cc. of a solution of streptomycin and Sulfamylon.*[8]

The patient was then placed in lithotomy position, and a triangular incision made about the anus. The levator ani muscles were sectioned far laterally. The anococcygeal raphe and urethra were divided, and the specimen consisting of anus, rectum, bladder, prostate and seminal vesicles was delivered from below. Several cigarette drains were placed in the perineal wound, which was partially closed with interrupted silk sutures. The patient received 2500 cc.

FIGURE 2. *Plastic Bags for the Collection of Feces and Urine.*

of whole blood and approximately 700 cc. of 5 per cent dextrose in water.

He had an uneventful convalescence. The temperature rose to a peak of 100°F. on one occasion during the entire postoperative course. The transverse colostomy functioned properly, and urine began to flow immediately from its distal end in quantities varying from 1000 to 1500 cc. daily. The clamp was removed from the sigmoid colostomy on the 3rd postoperative day, and thereafter gradually increasing amounts of urine began to flow from this orifice as well as from the distal loop of the transverse colostomy. By the 6th postoperative day the patient was receiving a full diet by mouth and was ambulatory on the 8th postoperative day. Postoperatively he received Dicumarol prophylactically. The

*Furnished through the courtesy of Winthrop-Stearns, Incorporated, New York City.

abdominal wound healed by first intention. The drains were gradually removed from the posterior wound, which closed rapidly without sepsis. The patient was fitted with plastic bags over both colostomies, the sigmoid bag being attached to the skin with water-tight cement (Fig. 1 and 2).

The nonprotein nitrogen, which was 38 mg. per 100 cc. on the 1st postoperative day, rose to 65 mg. on the 5th and then fell to 40 mg. per 100 cc. by the 15th postoperative day. On the 23rd day after operation, it had risen to a peak of 77 mg. per 100 cc. The plasma chloride was 113 milliequiv., the carbon dioxide 9.4 milliequiv., the serum sodium 146 milliequiv., and the serum potassium 3.4 milliequiv. per liter; the total serum protein was 6.32 gm. per 100 cc. A catheter was inserted into the distal colostomy and allowed to drain by gravity. At the same time daily intravenous therapy was administered for a few days in quantities of 2000 to 3000 cc. of 5 per cent dextrose in distilled water with added sodium lactate solution. The blood chemical values fell toward normal rapidly.

On the 30th postoperative day, when the patient was discharged from the hospital, the nonprotein nitrogen was 27 mg. per 100 cc., and the creatinine 2.62 mg. per 100 cc., and the carbon dioxide was 29.6 milliequiv. and the chloride 94.4 milliequiv. per liter. The urinary output was 1400 cc., and the total urinary chloride was 8 gm. measured as sodium chloride. An intravenous pyelogram showed good renal function with minimal dilatation of the calyxes and ureters (Fig. 3). At the time of discharge the posterior wound measured 2 by 2 by 6 cm. and was clean and granulating. When seen several weeks after discharge, the patient was asymptomatic, the posterior wound was completely healed, both colostomies were functioning well, and the nonprotein nitrogen was 39 mg. per 100 cc.

All cultures, including the segment of colon excised at operation, were smeared on a blood-agar plate and planted in beef-heart infusion broth enriched with sheep's blood and fortified with 5 mg. per 100 cc. of para-aminobenzoic acid. Chopped meat fortified with infusion broth was used for an anaerobic medium. Cultures of the colonic tissue were sterile after 48 hours, and at 72 hours yielded rare colonies of *Candida albicans* (*Monilia albicans*) and diphtheroid bacilli. None of the organisms observed in the cultures of colonic contents before treatment were present. Coliform counts done by a modification of the streak method of Poth[9] were 30,000 organisms per gram of feces on the 6th and 5500 per gram on the 2nd preoperative day.

Pathological examination revealed that the urethral perforation extended from the posterior portion of the prostatic urethra along a ragged tract through the tumor on the anterior rectal wall into the lumen. Grossly, the tumor surrounded both seminal vesicles and appeared to involve the posterior wall of the bladder although no tumor was evident upon the bladder mucosa. The prostate gland was not grossly involved by tumor.

Microscopical sections revealed poorly differentiated papillary adenocarcinoma. The tumor extended through the muscularis into the adventitia of the rectum and was seen in endothelium-lined spaces located in the adventitia and in the fibrofatty tissue in the space of Retzius. Microscopically, no tumor was seen to extend into the wall of the bladder, prostate or urethra. No tumor cells could be made out in the granulating tract of the perforation. A small polyp present in the rectum showed early carcinoma in situ. The lymph nodes examined were negative for tumor metastases.

Discussion

Proximal colostomy is a well recognized safety measure preliminary to anastomosis involving the lower alimentary tract. The logic of its use in the type of operation reported above is attested by the incidence and seriousness of complications following ureterointestinal anastomosis as reported in the literature.[1, 2, 10-12] These include urinary and urinary-fecal fistulas, uremia, acute pyelonephritis, hydronephrosis and sepsis of the abdominal and perineal wounds. Hinman and Weyrauch[10] reported that Nesbitt had suggested the principle of temporary colostomy for the purpose of sterilization of the lower bowel preliminary to ureteral implantation, and that in 1931 Higgins had applied this principle to dogs, irrigating the defunctionalized loop with Mercurochrome and boric acid. At the time of the report of Hinman and Weyrauch (1937) no clinical cases had been reported, and to our knowledge this principle has not come into clinical use since that time. A proximal colostomy not only affords diversion of the fecal stream but also prevents distention at the site of anastomosis. It accomplishes this with greater efficiency than a Miller–Abbott tube. The prompt response of fecal fistulas and wound sepsis to colostomy in these cases and the serious debilitating consequences of a leak at the ureterointestinal anastomosis suggest its routine use preliminary to any operation involving ureterointestinal anastomosis.

The greatest benefit derived from proximal colostomy is diversion of the fecal stream. In the presence of established wound sepsis following a leak in the anastomosis, this benefit is due to removal of the constant source of bacterial contamination rather than to elimination of the bulk of the fecal content. Therefore, the instillation of properly selected antibacterial agents in an attempt to sterilize the defunctionalized loop follows logically the use of a proximal colostomy. Treatment in the case reported above was planned to obtain a maximal reduction in the flora of the colon on the day of operation. The choice of antibacterial agents was guided by the sensitivity of the intestinal flora. Cultures taken just before operation were used to work out sensitivities to various antibiotics of the organisms remaining in the colon as now changed by intestinal antiseptic therapy. Fortunately, infection did not develop in this case, but with such advance information it should be possible to institute systemic or topical therapy with greater speed and specificity were infection to develop. Sulfathalidine was selected to be given with the chosen antibiotic in this case because it is superior to Sulfasuxidine in the presence of an enterostomy.[9] Because of the penicillin-Sulfathalidine antagonism demonstrated by Poth,[6] Sulfasuxidine was substituted on the last day before operation so that the patient could have the benefit of unimpeded penicillin prophylaxis.

The appearance of rare colonies of diphtheroids and *C. albicans* in the seventy-two-hour culture suggests contamination inasmuch as these organisms did not grow out in the original cultures. It therefore appears that a practical if not absolute sterilization of the bowel was achieved in this case.

The principles of ureterointestinal anastomosis emphasized by Cordonnier[4] appear sound and were utilized in this case. They are as follows: minimal mobilization of the ureters, transposition of the bowel rather than of the ureters, mucosa-to-mucosa anastomosis and elimination of the submucous

tunnel. It is not unlikely that reduction of the number of organisms to which the urinary tract is exposed is an important factor in the avoidance of ascending infection, although secondary in importance to the prevention of stasis. This, together with the facility with which the urine is collected from the patient's isolated loop of colon, and the desirability of a "dry" rather than a "wet" colostomy for fecal output have suggested that the distal opening of the transverse colostomy be closed. We have been deterred by the patient's wishes, however, and by the transient postoperative episode of nitrogen retention and hyperchloremia. Whether this episode was due to ureteral obstruction or to selective absorption of urinary constituents from the sigmoid loop is a matter for conjecture, but the intravenous pyelogram taken fifteen days postoperatively (Fig. 3) and the prompt response to replacement therapy suggest the latter as the most likely explanation. It is known that implantation of ureters higher in the intestinal tract does cause nitrogen retention.[13, 14] The question of the length or even the desirability of a loop of bowel as a urinary receptacle is unsettled. It may be necessary to restore colonic continuity by closing the patient's transverse colostomy and thus allowing faster emptying by virtue of increased peristalsis if further episodes of chemical and electrolytic imbalance develop.

Summary

A successful case of radical excision of pelvic viscera for complicated carcinoma of the rectum in a male patient is presented.

The principles of preliminary proximal colostomy and intestinal antisepsis by the instillation of properly selected antibiotic and chemotherapeutic agents are suggested as prophylactic measures against the postoperative complications of wound sepsis and urinary-fecal fistulas.

The patient re-entered the hospital in a semicomatose state on September 22. The nonprotein nitrogen was 178 mg. per 100 cc., and the serum chloride was 120 milliequiv., the carbon dioxide 5.23 milliequiv., the serum potassium 5.7 milliequiv., and the sodium 147 milliequiv. per liter. Infusions of sodium lactate, Butler's solution and dextrose and water were given daily. The isolated segment of bowel was perfused with a solution containing sodium, potassium and chloride in concentrations approximating those of the blood. The patient showed gradual clinical improvement, and after 23 days of this treatment the nonprotein nitrogen was 80 mg. per 100 cc., and the serum chloride was 116.3 milliequiv., and the carbon dioxide 18.2 milliequiv. per liter. It was not possible to restore further his chemical and electrolytic balance by these methods. On October 14 the transverse colostomy was closed, and the operation was followed by an uneventful convalescence. The patient took food and fluids orally in adequate amounts, and on November 9, the nonprotein nitrogen was 58 mg. per 100 cc., and the serum chloride 106.2 milliequiv., the serum potassium 5.84 milliequiv., the sodium 136 milliequiv., and the carbon dioxide 22.8 milliequiv. per liter. An intravenous pyelogram showed early appearance and fair concentration of the dye in both kidneys. There was slight blunting of the calyxes, with moderate dilatation of the renal pelves and ureters. The findings were essentially the same as those in the films taken 15 days postoperatively (Fig. 3) and suggested that the chemical and electrolytic changes were not on the basis of ureteral obstruction. When discharged at his own request

Figure 3. *Intravenous Pyelogram Taken Fifteen Days Postoperatively, Showing Minimal Dilatation of the Calyxes and Ureters.*

on November 16 the patient was asymptomatic, and the terminal colostomy was functioning well.

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ADRENOCORTICAL HYPOPLASIA IN THE NEWBORN INFANT*

Report of a Case with Replacement Therapy

R. William Provenzano, M.D.†

BOSTON

HYPOFUNCTION of the adrencortical tissue in the newborn infant presents a characteristic clinical syndrome. The manifestations that may result from temporary deficiency of this gland have been suggested by several authors.[1-8] No report has been found in the pediatric literature of such manifestations, however, with response on replacement therapy and confirmation of the diagnosis of simple hypoplasia of the adrenocortical tissue. It is the purpose of this paper to present the case of a newborn infant that demonstrates clinically hypofunction of the adrenocortical tissue and in which post-mortem examination established the existence of this condition.

My interest in the use of adrenocortical extract originated with its administration shortly after birth to a patient who had a temperature of 108°F. by rectum. The findings at this time were consistent with the diagnosis of bilateral atelectasis and cerebral hemorrhage. Because of the hyperpyrexia and shock-like appearance, it was believed that there might be some injury to the adrenal glands, owing either to anoxemic changes or to direct trauma. After the injection of hormonal extract,‡ the alveoli expanded, with improvement in respiration and clearing of the lung fields as demonstrated by auscultation. It was also noted that a clysis recently given was very rapidly absorbed. It is possible that adrenocortical extract

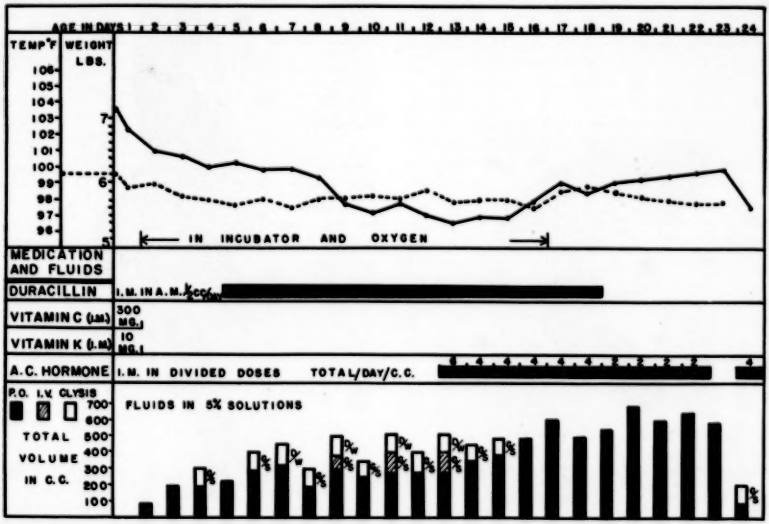

FIGURE 1. *Pertinent Clinical and Laboratory Data.*

*From the Pediatric Services of the Cambridge City Hospital, Cambridge, Massachusetts, and St. Elizabeth's Hospital, Brighton, Massachusetts.

†Visiting pediatrician, Cambridge City Hospital, St. Elizabeth's Hospital and Sancta Maria Hospital; consultant and chief-of-pediatrics, Harley Hospital; consultant in pediatrics, Longwood Hospital.

‡Adrenocortical extract, a biologically standardized extract is prepared from adrenal glands containing the cortical activity that is essential for life. Each cubic centimeter contains not less than 50 dog units or 2.5 rat units. This product was supplied by the Upjohn Company through the courtesy of H. F. Hallman, M.D., Ph.D., Medical Division.

aided in the absorption of the pulmonary fluid, with resultant expansion of the lung fields. In the course of clinical investigation of the subject, improvement was noted after the administration of adrenocortical hormone in newborn infants with anoxemia, prematurity and atelectasis. The clinical response warrants mention, and the experimental use of the hormone in these conditions will be described in another publication upon completion of the present studies.

The patient described below is reported because of the relation between clinical symptoms, results of specific therapy and pathological evidence of obvious adrenocortical deficiency.

Case Report*

After a period of uneventful gestation a male infant was delivered without difficulty. The initial examination in the delivery room showed no abnormalities. The infant appeared active, with a lusty cry, good color and normal respirations. The birth weight was 7 pounds, 11½ ounces. Eleven hours later, the infant had become listless, with a weak cry, and showed weak response to stimulation. The Moro reflex was diminished, and the sucking reflex was inadequate. There

Figure 2. *Cross Section of the Right Adrenal Gland (Hematoxylin and Eosin Stain x6). The cortex is the outermost gray band.*

was marked loss in weight with dehydration and acidosis. There were no loose stools, no evidence of infection and no jaundice. On the 4th postnatal day, because of marked weight loss and dehydration, with inanition fever, a clysis of 120 cc. 5 per cent glucose in saline solution was given. This was absorbed slowly in spite of the severity of dehydration. The respirations became shallow and rapid. Attacks of cyanosis occurred. Oxygen was administered in a heated incubator, but shock symptoms continued in spite of symptomatic treatment. Aggravation of the respiratory symptoms followed, and increased moisture was found throughout both lung fields. Because of the pulmonary findings penicillin was administered prophylactically. Repeated clysis and intravenous administration of fluids were ineffective in keeping the patient hydrated and his respiratory difficulty, weight loss, listlessness and irritability increased.

*Reported through the courtesy of Dr. Philip McGovern, of Cambridge, Massachusetts.

On the 13th postnatal day, because of the patient's general debility, weight loss to 5 pounds, 6 ounces, and progression of symptoms to the point of collapse, 2 cc. of adrenocortical hormone was given and repeated in 1 hour. The patient's condition remained unchanged. In 4 hours the treatment was repeated. At this time (5 hours after therapy) the parient was more alert and active, and less fretful. Cyanosis and dyspnea diminished, both being absent within 6 hours of hormone therapy. The patient did not require any further oxygen although it was continued prophylactically. The sucking reflex became active. Food was taken and well tolerated. At this time 2 cc. of adrenocortical hormone was administered every 12 hours. Hydration was maintained without parenteral injection of fluid, clyses becoming unnecessary on the 3rd day after therapy was started. Weight gain continued, and

Figure 3. *Essentially Normal Adrenal Gland of a Twenty-Six-Day-Old Child (Hematoxylin and Eosin Stain x6).*

after 10 days of treatment with adrenocortical extract, the weight was 6 pounds, 3 ounces. The clinical response to adrenocortical hormone is presented in Figure 1.

To establish the etiologic factor it was decided to omit adrenocortical-hormone therapy. Within 14 hours, the patient began again to show evidence of irritability, listlessness and pallor. He refused to suck on the nipple. Bouts of cyanosis recurred, and oxygen therapy became necessary. The respirations became rapid and shallow. These signs were similar to those prior to hormone treatment. Vasodilatation with blotchy appearance of the skin, which was cool and moist with diminished turgor, was also evident. Slight tremors of the upper and lower extremities occurred. Bilateral circular nystagmus was present. In spite of symptomatic therapy and adequate parenteral administration of

fluids, there was progressive evidence of dehydration, generalized weakness and debility. A convulsion occurred 22 hours after removal of the hormone. The convulsive seizure was at first unilateral and focal, involving the left ocular and facial muscles. It then spread to the left arm and leg and rapidly became generalized. There was marked rotary nystagmus. The seizure resembled that often seen in a patient with tetany of the newborn or hypoglycemia. There was no opisthotonos. Adrenocortical extract was again resumed, and at this time 4 cc. was given and repeated in 1 hour. In spite of active treatment, convulsions continued and within 2 hours the patient died.

The patient's blood was Group O and Rh+. Blood cultures on the 6th, 8th and 13th days of life showed no growth. Examination of the blood on the 6th, 9th and 13th days, respectively, revealed red-cell counts of 5,190,000, 4,500,000 and 4,900,000, with hemoglobin values of 100, 92 and 96 per cent (Sahli), and white-cell counts of 26,550, 11,400 and 33,600; the differential counts in these 3 days were as follows: neutrophils, 46, 49 and 46 per cent; lymphocytes, 40, 32 and 42 per cent; myelocytes, 12, 18 and 10 per cent; and eosinophils, 2 (6th day) and 1 (13th day) per cent (there were 1 per cent myelocytes on the 9th day). On the 8th and 13th days the nonprotein nitrogen was 62 and 58 mg. per 100 cc., and the blood sugar 70 and 170 mg. per 100 cc.; the total protein on the 8th day was 4.2 gm. per 100 cc. On the 9th day the carbon-dioxide content was 25 vol. per cent, and the calcium 8.1 mg. and the phosphorus 5.8 mg. per 100 cc., and the phosphatase 11 Bodansky units per 100 cc. On the 10th and 21st days the serum sodium was 153 and 139 milliequiv., the serum potassium 2.54 and 3.1 milliequiv., and the serum chloride 137.8 and 104.1 milliequiv. per liter. Urinalysis was essentially negative except for + tests for albumin on the 6th, 8th, 14th and 18th days of life. Spinal tap yielded no abnormal findings.

Post-mortem examination* revealed a moderately well developed, somewhat emaciated infant weighing 1119 gm. and measuring 49.5 cm. in length. There was no abnormal pigmentation of the skin, and there was no edema. The organs that showed pathologic changes were the lungs and adrenal glands. The lungs had a bronchopneumonic process involving about a third of the parenchyma. Histologic examination showed an infiltration of the bronchial spaces, alveolar space and walls by polymorphonuclear leukocytes, with some deposit of fibrin and a serum precipitate. Scattered throughout the lung sections were areas of atelectasis. The adrenal glands were greatly reduced in size — the left weighed 1.3, and the right 1.8 gm. The cortex was yellowish but of paper thinness. The left adrenal gland showed considerable irregularity in its shape, containing several isolated lobules of cortical tissue. The medulla appeared adequate in amount and was quite distinct from the cortex. Histologic studies revealed that the cortex, in the narrowest zone, was eight cells deep. The cortex showed a fairly mature type of differentiation into the glomerular and fascicular zones. The cortical cells contained a moderate amount of lipoid material, most prominent in the fascicular zone as indicated by the scarlet-red stain. The medulla also contained a moderate number of cells with lipoid material composed of various-sized globules. The right adrenal gland (Fig. 2) is compared with that of a normal infant (Fig. 3).

The size, weight and microscopic findings of these adrenal glands indicated a marked hypoplasia. The normal weight for an infant of twenty-five days is + 5 gm.[9] The differentiation of cortex in this patient approached that of a mature adrenal gland.

*Performed by Dr. Reuben Z. Schulz, pathologist-in-chief, Cambridge City Hospital.

Discussion

The patient in this case showed adrenocortical deficiency immediately after birth, with signs and symptoms characteristic of that condition: listlessness, irritability, anorexia, vomiting, grayish hue to skin, general muscular weakness, as manifested by poor respiratory muscular action (dyspnea, cyanosis and pulmonary congestion), diminished Moro reflex, diminished grasp and poor sucking reflex, weight loss, dehydration, acidosis and convulsions.

The post-mortem findings indicate that an organic deficiency of adrenocortical tissue can occur in the newborn infant, with clinical evidences becoming apparent shortly after birth. Conceivably, varying degrees of deficiency may occur, the symptoms depending upon the amount of adrenocortical hormone that may be deficient. It may be temporary and compatible with life[5, 6] or fatal. One of the factors contributing to the death of the patient in the case reported above was acute bronchopneumonia, which probably further increased the requirement for adrenocortical hormone and thereby further depleted the already insufficient amount of this substance.

The symptoms likewise may differ, depending upon the time of onset. If they occur shortly after birth, those of hydration and muscular and respiratory functions may be noted. If there is a delay in onset, there may be similar symptoms, but outstanding among them will be those that single out the gastrointestinal tract. It is possible, from the action described, that the hormone exerts "initial selective affinity" for a certain system when it first exerts its action — that is, concentrating upon one system at birth, and another with growth and development.

Symptoms such as listlessness, initial newborn debility and weight loss may be due to a transitory and temporary deficiency of the adrenocortical hormone. In the patient described, these symptoms did occur to a marked degree.

Summary

A case of adrenocortical hypoplasia in a newborn infant is presented. The clinical signs are described, and the beneficial effects of replacement therapy are analyzed. The post-mortem findings confirmed the diagnosis.

The beneficial results of the use of adrenocortical extract in newborn infants with anoxemia, atelectasis and prematurity are mentioned in the hope of stimulating further study to evaluate the importance of this hormone in pediatrics.

520 Commonwealth Avenue

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THE EFFECT OF 10 PER CENT AND 100 PER CENT OXYGEN INHALATION ON CERTAIN LIVER-FUNCTION TESTS*

PAUL KAUFMAN, M.D.,† JULIUS HOLLO, M.D.,‡ JULIUS ROSENTHAL, M.D.,§ JACOB STONE, M.D.,¶ R. DONALD BECK, M.D.,|| AND VICTOR FINK, M.D.**

With the Technical Assistance of Harry Wulfson, A.B.

NEW YORK CITY

AS EARLY as 1926, evidence was presented by Resnik and Keefer[1] that dogs subjected to anoxia were more easily jaundiced by carbon tetrachloride than the control animals. Since then, several authors,[2-4] using different approaches, furnished additional data indicating that anoxia in its different forms might disturb certain functions of the liver and cause liver damage. Since most of these experiments were done on animals, and since the ones on human beings were carried out after surgical procedures and anesthesia, it seemed a logical step to examine the problem in human beings with moderate liver disease by the most direct method, the inhalation of 10 per cent and 100 per cent oxygen. The problem was to determine whether the inhalation of 10 per cent oxygen and 90 per cent nitrogen mixture or inhalation of 100 per cent oxygen influenced liver-function tests.

METHODS

Group I

A mixture of 10 per cent oxygen and 90 per cent nitrogen was administered by mask for thirty-five minutes. Five minutes after the beginning of the inhalation 5 cc. of bromsulfalein solution (containing 50 mg. per cubic centimeter) was injected in the antecubital vein; thirty minutes later†† blood was withdrawn, and the retention compared with the result of the control bromsulfalein test done a few days earlier. The dose of the dye was not adjusted to the weight of the patients, since many of them had ascites or edema because of liver disease, and since the difference in retention before and after inhalation rather than the amount retained was the significant factor in the experiments. No ill effect of the anoxia test was noticed as shown by direct electrocardiograms in a few cases and by clinical signs in the others. Nor did the injection of the dye cause untoward symptoms.

TABLE 1. *Effect of Inhalation of 10 Per Cent Oxygen for Thirty-Five Minutes on Bromsulfalein Retention.*

Case No.	Age	Sex	Diagnosis	Control Test	Anoxia Test	Interval between Tests
	yr.			%	%	days
1	49	F	Laënnec's cirrhosis	5*	20*	2
2	35	F	Laënnec's cirrhosis	10*	15*	3
3	52	F	Arsenical hepatitis	15	30	2
4	38	F	Laënnec's cirrhosis	20	20	2
5	48	M	Laënnec's cirrhosis	10	20	4
6	49	F	Laënnec's cirrhosis	15	30	3
7	51	F	Laënnec's cirrhosis	15	40	2

*Blood samples were withdrawn 30 minutes after injection of the dye except in these cases, in which the sample was taken 45 minutes after injection.

Group II

In this group 100 per cent oxygen was administered also by mask for four hours, and the excretion of the bromsulfalein tested at the end of the inhalation period and compared with the control test done a few days before. It should be added that in some cases the same patients were used for experiments in the two groups. A total of fourteen experiments — seven for each group — were done.

It should be noted that at the beginning of the experiments in a number of cases the effect of anoxia and hyperoxia on other liver-function tests was also examined. The type and the number of these tests were as follows: prothrombin time in 4 experiments, alkaline phosphatase in 4, cephalin flocculation in 12, bilirubin in 13, and urinary urobilinogen in 12. There was no consistent pattern

††In 2 cases forty-five-minute tests were done.

*From the Second Medical Division, Goldwater Memorial Hospital. The anoxia and hyperoxia apparatus described were kindly supplied by Keefe and Keefe Oxygen Supply Company, New York City.

†Attending physician in charge of medical service, Second Medical Division, Goldwater Memorial Hospital.

‡Associate attending physician, Second Medical Division, Goldwater Memorial Hospital.

§Pathologist, Second Medical Division, Goldwater Memorial Hospital.

¶Assistant resident physician, Second Medical Division, Goldwater Memorial Hospital.

||Director, Second Medical Division, Goldwater Memorial Hospital.

**Resident physician, Second Medical Division, Goldwater Memorial Hospital.

in the results of this part of the study. The possible cause for these negative results is discussed below.

The 10 per cent anoxia test was not used in any patient who had evidence of advanced arteriosclerosis, decompensated cardiovascular disease or recent or old myocardial infarction. Also, patients with very far advanced liver damage were eliminated, especially for the anoxia test.

Results

In the first group (Table 1) the anoxia caused significant changes in the bromsulfalein excretion in 5 of the 7 cases. The patient in Case 1, a forty-nine-year-old woman with Laënnec's cirrhosis, showed 5 per cent retention on May 9, 1948. Two days later on 10 per cent oxygen inhalation, the retention rose to 20 per cent. Another patient (Case 3), a thirty-five-year-old woman with arsenical hepatitis, originally had 15 per cent retention; two days later with anoxia the dye retention increased to 30 per cent. In Case 7 the retention increased from 15 to 40 per cent after anoxia. Another patient (Case 2), a thirty-five-year-old woman, showed a minor change from 10 to 15 per cent. There was no change in Case 4; the patient had a 20 per cent base line, and the retention of the dye remained 20 per cent after anoxia. In summary, there were significant changes in 5 cases, minor change in 1 and no change in 1.

In the second group (Table 2) the patients received 100 per cent oxygen for four hours. Case 8 showed a change from 10 per cent to "no dye," and Case 9 a decrease from 25 to 10 per cent. In Case 10 the retention changed from 10 per cent to "no dye." Case 11 showed a change from 40 to 30 per cent, and Case 12 from 25 to 5 per cent retention. Cases 13 and 14 remained unchanged on the inhalation. The tests in this group, therefore, showed significant changes in 4 cases, minor change in 1, and no changes in 2.

Discussion

The results in this small number of cases indicate that the inhalation of 10 per cent oxygen and 90 per cent nitrogen mixture for thirty-five minutes impaired the excretion of bromsulfalein in most patients to a significant degree. Minor or no changes were noted in the remainder; no contrary results — that is, improvement in the excretion of the dye on anoxia — were found. Since the retention in tests on certain subjects was at the upper limit of normal, and anoxia brought it into an abnormal range (Table 1), this aspect of the problem suggests further study of the possibility of a test for incipient liver damage. The effect of 10 per cent oxygen inhalation in normal subjects is shown in Table 3.

The impairment of the bromsulfalein excretion during anoxia was not due to blockage of the Kupffer cells by the dye employed in the control test, since a sufficient time elapsed between the control test and the post-anoxia test for the liver to have handled the control test dose of the dye. Moreover, the liver function improved on 100 per cent oxygen administration despite the fact that a control test dose of the dye was also used in this study. Since almost all patients were nonicteric and had low serum bilirubin levels, the bromsulfalein test was a measure of the liver function. Thus, the changes were not due to faults inherent in the tests, but rather reflected impaired liver func-

Table 2. *Effect of Inhalation of 100 Per Cent Oxygen for Four Hours on Bromsulfalein Retention.*

Case No.	Age	Sex	Diagnosis	Control Test	Anoxia Test	Interval between Tests
	yr.			%	%	days
8	35	F	Laënnec's cirrhosis	10*	"No dye"	8
9	49	F	Laënnec's cirrhosis	25*	10	2
10	52	F	Arsenical hepatitis	10	"No dye"	5
11	61	F	Laënnec's cirrhosis	40	30	1
12	65	M	Laënnec's cirrhosis	25	5	7
13	51	F	Laënnec's cirrhosis	20	20	6
14	49	F	Laënnec's cirrhosis	25	25	6

*Blood samples were withdrawn 30 minutes after injection of the dye except in these cases, in which the sample was taken 45 minutes after injection.

Table 3. *Effect of Inhalation of 10 Per Cent Oxygen for Thirty-Five Minutes on Bromsulfalein Retention in Normal Subjects.**

Subject No.	Age	Sex	Bromsulfalein Retention	
			Before Inhalation	After Inhalation
	yr.		%	%
1	76	M	4	0
2	54	M	3	3
3	46	M	0	0
4	81	M	0	4
5	62	M	2	3
6	90	M	0	1
7	58	M	5	2
8	61	M	1	0
9	51	F	2	1
10	69	F	2	0
11	53	F	3	0
12	58	F	2	3
13	46	F	0	0
14	56	F	2	1

*These tests were done on inmates of the New York City Home, which is under the medical supervision of Goldwater Memorial Hospital. None of the subjects had clinically demonstrable liver disease or cardiac congestion of the liver. The figures indicate no significant changes under anoxia.

tion from anoxia and improvement in liver function from 100 per cent oxygen administration.

This effect of anoxia may partially explain the changes in liver function occurring during prolonged shock and also after surgical procedures under anesthesia. It is also suggested that the inability of patients with active hepatitis to tolerate physical exercise and the impairment in liver-function tests produced by exercise in such patients, may be partially explained by liver anoxia.

Other liver-function tests, among them cephalin flocculation, gave inconsistent results. This is not surprising, since cephalin flocculation is an index of active disease of the liver parenchyma and is not a test of the functional capacity of the liver. The positive results of bromsulfalein excretion and the negative results of cephalin-flocculation tests on anoxia confirm the data of Tagnon and his associates,[2] who found the same trend in both tests after surgical operations under anesthesia.

On 100 per cent oxygen inhalation, the bromsulfalein excretion improved significantly in 4 of the 7 cases. One showed minor change, and 2 did not show any change. No cases showed the opposite trend — that is, impairment of dye excretion — after 100 per cent oxygen administration. The therapeutic potentialities of the inhalation of 100 per cent oxygen administered in a more prolonged way than in the tests under discussion also deserves further investigation. This procedure served well as an additional control of the results of the anoxia tests.

Hurtado[5] reported increased bilirubin in the blood of 12 normal natives in Peru living under high-altitude anoxia conditions. Engel and his associates[6] found that the liver of rats withstood the anoxia up to forty-five minutes; longer exposure caused irreversible damage. On human beings in the present tests, the effect of thirty-five minutes of anoxia on total serum bilirubin was inconclusive. In our study the blood bilirubin, cephalin flocculation, prothrombin time and urinary urobilinogen and alkaline phosphatase tests gave negative results with both anoxia and hyperoxia. The reason for this might be that the functions of the liver indicated by these tests in man are less sensitive to changes in the oxygen supply than the functions shown by the bromsulfalein clearance. It is possible that the time of thirty-five minutes of anoxia or four-hour hyperoxia was too short to demonstrate potential effects of varying oxygen supply on these tests.

Summary

In patients with impaired liver function the breathing of 10 per cent oxygen and 90 per cent nitrogen mixture for thirty-five minutes impaired bromsulfalein excretion to a significant degree.

Breathing of 100 per cent oxygen for four hours improved in certain cases the excretion of the dye.

Other liver-function tests done in combination with anoxia and hyperoxia gave inconclusive results.

The need of further investigations of the diagnostic value of anoxia and of the possible therapeutic value of prolonged hyperoxia in liver disease is discussed.

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MEDICAL PROGRESS

UROLOGY

FLETCHER H. COLBY, M.D.*

BOSTON

RECENT advances in urology include studies of the renal blood supply, the effects of renal ischemia, and investigations into the causes and treatment of renal insufficiency. Studies of the physiology of the ureter have shown how this organ reacts under varying conditions and have disproved many mistaken beliefs of the past. Advances also have been made in the operative management of certain lesions of the genitourinary organs.

RENAL BLOOD SUPPLY

The presence of more than one pathway for the circulation of blood within the kidneys has been considered a possibility since Bowman's studies of the renal circulation in 1842. Nonglomerular arteriovenous anastomoses in the kidney have frequently been demonstrated. The mechanism and significance of these anastomoses, however, were not understood until the recent studies on the renal circulation by Trueta and his associates.[1]

During the 1941 air raids in England, it was observed that certain patients suffering from the "crush syndrome" in whom there had been continuous pressure of one or more limbs developed progressive impairment of kidney function and sometimes died from renal failure. Trueta believed that the injury might have caused spasm of the arteries of the damaged extremity and that the arterial spasm might involve the renal arteries. Animal experiments were then conducted that showed under these conditions a reduction in the caliber of the renal artery and a reduced blood flow to the kidney.

Trueta's attention was then directed to the circulation within the kidney. After stimulation of the left sciatic nerve, it was observed that the cortex of the left kidney received a considerably smaller amount of blood than the medulla. Direct observations on the exposed kidney showed that the surface of the kidney became pale and that red blood appeared in the renal vein. This experiment confirmed the existence of a short-circuiting mechanism in the kidney and showed that this mechanism could be brought into operation by a neurovascular reflex. A diversion of the renal blood from the cortex through a pathway in the medulla was the logical explanation of this phenomenon. Studies were then made to discover the anatomic channels through which the blood flowed when it was diverted from the cortex of the kidney.

Studies of intrarenal blood flow in animals suggested that the blood vessels of the cortex in the normal animal receive a greater part of the renal blood supply than the blood vessels of the medulla. In the stimulated animal, however, the blood vessels of the medulla received the greater part of the renal blood supply while those of the cortex received little or no blood. The blood vessels in the medulla that carried this increased amount of blood were thought to be the vasa recta.

Little interest had previously been shown in this portion of the intrarenal vascular system. Injection experiments in the past had defined poorly the blood vessels of the medulla of the kidney. Standard descriptions of the intrarenal blood supply depict interlobular arteries arising from the arcuate arteries. From the interlobular arteries afferent arterioles go to the glomeruli. The efferent vessels of the glomeruli in most of the renal cortex go to an intertubular capillary network, which drains into an interlobular vein. The efferent vessels of glomeruli near the medulla, however, form a group of straight parallel vessels that course toward the apex of the medulla. These are the vasa recta. Through the vasa recta flows the blood when it is diverted from the renal cortex. Although much of the evidence for these facts was obtained by experiments on rabbit kidneys, the authors believe the same features are present in the human kidney.

The studies of Trueta and his associates appear to show that when blood is diverted from the renal cortex to the medulla, the vessels that constitute the medullary by-pass are as follows: the proximal parts of the interlobular arteries; the afferent arterioles of the juxtamedullary glomeruli; the glomeruli of the cortex nearest the medulla and their efferent vessels; the "arterial" and venous components of the vasa recta within the medulla; and the proximal parts of the interlobular veins.

Trueta concluded from his experiments that prolonged constriction of a hind limb caused less blood to reach the kidney through a reflex neurovascular mechanism and that the distribution of blood within the kidney might be so changed that the cortex received little or no blood. Cortical ischemia was apparent visually and by angiograms. At the same time, blood circulated through the medulla, and red blood was observed in the renal vein. It was

*Chief, Urological Service, Massachusetts General Hospital.

concluded that the intrarenal blood flow does not follow an unchangeable pattern but circulates through two chief channels, cortical and medullary. The vessels of the medullary pathway are those associated with the glomeruli nearest the medulla, and the vasa recta form the major portion of the vascular supply of the medulla. Blood may pass through one or both of these vascular pathways within the kidney. An example in the human kidney of the medullary pathway carrying the blood within the kidney is seen in bilateral cortical necrosis.

This work appears to be a definite contribution to the understanding of the circulation of the blood within the kidney. It is questionable, however, that it accounts for the anuria that sometimes accompanies the "shock-syndrome."[2]

The effects of temporary occlusion of the renal blood supply have been studied by several investigators. Van Slyke et al.,[3] in experiments on the dog, found that if one kidney was removed and the renal artery of the other kidney was clamped for three hours, the animal recovered after an elevation of the blood nitrogen. When the renal artery was occluded for four hours, half the dogs recovered. Clamping the renal artery for six hours proved uniformly fatal, with death from uremia in four to eight days. Occlusion of the remaining renal artery for more than four hours caused irreversible changes.

Complete renal ischemia in rats for two hours was found to be uniformly fatal.[4] The mortality at ninety minutes was 73 per cent. Most animals survived a period of thirty minutes of complete renal ischemia. The principal change in the kidney was found to be necrosis of the descending segments of the proximal convoluted tubules, and the renal lesion was said to be unlike that observed in the crush syndrome.[4]

Renal Insufficiency

Considerable interest has been shown in the crush syndrome since its description in 1941 by Bywaters and Beal and in the uremic syndrome that follows severe injuries and incompatible blood transfusions. Some have considered that this syndrome was due to a toxin derived from damaged muscle or hemolyzed red blood cells. Others have suggested that it might be due to renal anoxia from diminished blood supply to the kidney. Badenoch and Darmady[5] considered that temporary partial occlusion of the remaining renal artery in the unilateral nephrectomized rabbit caused renal changes comparable to those observed in human traumatic uremia. Partial occlusion of the remaining renal artery in these animals maintained for two hours resulted in irreversible damage to the kidney followed by death. The first renal lesions produced were in the ascending and descending loops of Henle.

Van Slyke[6] studied the effects of shock on the kidney and found that an immediate effect of shock due to hemorrhage, trauma or dehydration is a decrease in renal blood flow and renal function, sometimes with complete anuria. If blood-volume loss is not severe, renal blood flow and function may be only temporarily decreased. If, however, shock is severe, constriction of the renal vessels occurs, and anuria may be present even with an arterial blood pressure as high as 100 . This is the first phase of the shock kidney. If renal ischemia does not last too long, there is no damage to the kidney.

If severe renal ischemia lasts sufficiently long, the second phase of the shock kidney occurs, and renal damage is present. The cells of the loops of Henle and the distal tubules show the most obvious damage, and there is impairment in tubular reabsorption. Even after several days of post-shock anuria, recovery may take place. In fatal cases anuria persists, and death from uremia occurs in from two to twenty days.

Treatment advised for shock anuria is immediate restoration of blood volume by blood transfusion, plasma or saline solution. Adequate amounts of bicarbonate are given if acidosis is present. Plasma chloride concentration is maintained. Overhydration is avoided to prevent circulatory embarrassment. A diet high in carbohydrate and fat and low in protein is given if nitrogen retention increases. The artificial kidney may aid in restoring renal function.

Post-traumatic renal insufficiency was studied among battle casualties, with a detailed and excellent report of the clinical, physiologic and biologic features of this syndrome and its treatment.[7] Cases included were those with a nonprotein nitrogen level of 65 mg. per 100 cc. or more, patients with oliguria for a period of at least twenty-four hours, and patients with a similar period of anuria.

These observers found that any patient who develops anuria under these circumstances has an extremely grave prognosis, the mortality being 91 per cent. Mortality was high also among those with oliguria — 47 per cent. In the patients with "high azotemia," mortality was 69 per cent. These figures illustrate the seriousness of this syndrome.

Renal failure was most common in patients with severe shock although it was not clear that the severity of the renal lesion was entirely determined by the degree of shock. The time factor among the patients in whom uremia was the primary cause of death was significant in that 41 per cent died in the first five days, and 50 per cent in the second five days — a total of 91 per cent within the first ten days. If these patients could be carried through this critical ten-day period, it was believed that they had a fair chance of recovery

The important biologic and physiologic abnormalities in the blood in post-traumatic renal insufficiency were nitrogen and phosphorus re-

tention, acidosis, hypochloremia and increase in plasma volume. These were evidences of diminishing renal function with inability to concentrate urine, failure to adjust for acidosis or alkalosis, and low tests of renal function. A progressive acidosis was characteristic with a falling plasma carbon dioxide combining power. There was evidence that the excretion of sodium as sodium bicarbonate was poorly effected in cases with alkalosis resulting from excessive administration of base. Hypochloremia was severe and progressive, largely as a result of inadequate salt intake although mortality was the same in the hypochloremic and normal chloride groups.

Total plasma volume was elevated in 22 of 23 patients with post-traumatic renal insufficiency, and 19 of them died. The degree of plasma-volume increase was related to fluid intake. Water retention seemed to be largely the result of the administration of more fluid than the impaired kidneys could excrete. Unexplained extrarenal factors that interfered with the maintenance of a normal extracellular fluid volume seemed also to be present. The administration of excessive fluids to patients with increased extracellular fluid volume, therefore, could cause fatal pulmonary edema rather than stimulating the kidneys to excrete.

As the syndrome progressed ability to concentrate urine diminished, and urine specific gravity became fixed in all patients with any marked degree of renal failure. This was one of the most striking and constant features of this syndrome and one of the earliest changes to appear. Ten of 73 patients with "high azotemia" and severe renal failure developed a diuresis and recovered. This was regarded as an important clue to proper treatment by affording the kidneys an opportunity for spontaneous recovery.

Treatment of post-traumatic renal insufficiency is considered largely one of prevention — that is, adequate treatment of shock. Shock appears to be the important factor in etiology. Once the syndrome is established, treatment is disappointing. The administration of too much fluid is to be avoided in order that the circulation be not overloaded, with resulting cardiac failure and pulmonary edema. A daily fluid intake for patients with oliguria or anuria should not be over 500 to 1000 cc. Fluid intake should roughly parallel fluid output if urine volume reaches 1 or more liters in twenty-four hours. Fluid by mouth is better than fluid parenterally. Parenteral fluid is given slowly as 5 or 10 per cent glucose in distilled water. No drugs were helpful in improving renal function. The important feature in treatment is to tide the patient over the critical period of renal failure until the kidneys spontaneously recover.[7]

In the treatment of renal insufficiency, Thorn[8] emphasized the fact that this condition should be regarded as a self-limited disease. Patients with mild cases due to intravascular hemolysis usually recover if treated conservatively. Excessive administration of fluids and salt is likely to aggravate edema of the interstitial spaces and prolong renal failure. Uremia may be relieved by the artificial kidney, but only patients who can regenerate adequate functioning renal tissue will recover by increasing the survival period.

During the emergency period of this syndrome, blood volume should be restored. Fluids should be restricted to minimum needs during the maintenance period, and the patient should be digitalized at the first sign of cardiac failure. The artificial kidney should be used in the more prolonged cases of renal failure to remove retained metabolites from the body. With the onset of diuresis excessive loss of sodium chloride is a danger, and it is important to follow the serum chloride level during this period and to administer adequate amounts of sodium chloride.[8]

Physiology of the Ureter

There have been many unanswered problems concerning the physiology of the human ureter and conflicting reports about the nerve mechanism that controls ureteral activity. It has frequently been claimed that certain drugs stimulate the ureter to contract or cause relaxation of the muscular wall. Some facts about the physiology of the ureter that have been generally accepted apparently have been based on inaccurate experimental evidence. Lapides[9] has made a significant contribution to a better understanding of the physiology of the intact human ureter in a series of well controlled experiments.

Studies to determine the normal physiology of the human ureter were conducted on patients with normal urinary tracts by means of ureteral catheterization. Observations were made to determine the effects of mechanical stimuli on ureteral peristalsis, the effect of blocking nerve impulses on the contractions of the ureter, the results of stimulation of the sympathetic and parasympathetic nervous systems upon ureteral activity, and the effects of drugs in stimulating the ureter to contract or in causing relaxation. *Through these experiments, a careful record was kept of urine-volume output.*

Studies on the effects of mechanical stimuli on ureteral contractility demonstrated that stretching of the ureteral muscle will initiate and vary peristaltic activity. Normally, pressure within the ureter is altered by the volume of urine excreted by the kidney, if intra-abdominal pressure and peripheral resistance (decreasing the caliber of the outflow valve on the apparatus measuring pressure within the ureter increases resistance) remain constant, an increase in urine volume causes increased intraureteral pressure and an increase in the amplitude of peristaltic contractions. Decreasing the urine output causes a decrease in intraureteral pressure and a decrease in the frequency and am-

plitude of contractions. This is in agreement with previous observations that the peristaltic activity of the ureter is governed by the degree of distention of the wall of the ureter by urine and that the stimulus for ureteral peristalsis is diuresis.

The effect on ureteral peristalsis of blocking the autonomic ganglions was obtained by the administration of tetraethyl ammonium chloride intravenously. By this drug both the sympathetic and parasympathetic nerve supplies to the ureter were blocked. Peristaltic activity after the administration of this drug was affected only by changes in urine volume. The effects of high spinal anesthesia, atropine and transentin were similar. It was concluded, therefore, that the ureter is able to carry on peristaltic activity without an extrinsic nerve supply.

Stimulation of the sympathetic fibers by epinephrine and of the parasympathetic system by Doryl and Prostigmine had no direct effect upon the contraction of the ureteral muscle. Changes in ureteral peristalsis were always dependent upon changes in urine volume produced by these drugs. The activity of the ureteral musculature appeared to be unaffected by the autonomic nervous system. The administration of curare did not affect ureteral peristalsis. Ureteral peristalsis, therefore, continued despite interference with the extrinsic nerve supply of the ureter. It is therefore reasonable to believe that the peristaltic contractions of the ureter do not originate from impulses from the central nervous system but that the nerve supply contains only vasomotor and sensory fibers.

The administration of such drugs as amethone, depropanex, calcium levulinate, Demerol, lipolutin, morphine, papaverine, perparin, nitroglycerin, amyl nitrite, Benadryl, transentin, atropine and Pitressin had no effect upon ureteral tone or peristalsis. Ureteral activity was uninfluenced by the intraureteral injection of papaverine or Avertin. Any changes in ureteral peristalsis occurring after the administration of any of these drugs could be attributed directly to changes in urine output. If the urine-volume output was constant, there was no change in ureteral tone or peristalsis as a result of the administration of any of these drugs. Morphine produced no increased tone or peristalsis of the ureter although this is contrary to opinions previously expressed. Since morphine has no such effect it may be used safely to relieve the pain of ureteral colic without causing spasm of the ureter. None of the drugs in common usage were found effective in decreasing the tone or peristalsis of the ureter.

From these studies it seemed apparent that ureteral peristalsis is initiated as soon as urine flows into the renal calyxes. As urine output increases ureteral peristalsis increases. Decreased urine output is accompanied by decreased ureteral peristalsis. The factor that is the normal adequate stimulus for rhythmic contractions of the ureter is urine volume mechanically stretching the muscle fibers of the ureter. Ureteral peristalsis, therefore, appears to be entirely independent of the central nervous system and is unaffected by any known drug.[9]

Thoracoabdominal Nephrectomy

The removal of large renal neoplasms is often a difficult surgical procedure. In the past, such tumors have been approached through either a lumbar or a transperitoneal incision. It was generally considered that the transperitoneal approach had certain advantages for the removal of large tumor masses since by this route the renal blood supply could be ligated with less manipulation of the neoplasm. There seemed less likelihood, therefore, of squeezing tumor cells into the large collateral veins that usually accompany tumors of the renal parenchyma. Transperitoneal nephrectomy for these tumors, in spite of certain advantages over the lumbar route, however, was frequently unsatisfactory. Large tumors often grew over the renal pedicle or so displaced the renal vessels that their identification was extremely difficult. Considerable hemorrhage was not an uncommon accompaniment of these operations. Attempts to remove large renal neoplasms through a lumbar incision, with removal of the twelfth rib, were often even more hazardous and at times impossible.

Recognition of these difficulties led to the investigation of other practical methods of removing a kidney under difficult circumstances, particularly large neoplasms of the renal parenchyma. In 1948 Mortensen,[10] of Australia, reported the successful removal of a large tumor of the left kidney through a transthoracic, transdiaphragmatic approach. About six months previously an unsuccessful attempt had been made elsewhere to remove this tumor through a transperitoneal incision. Excessive bleeding at the first operation necessitated leaving clamps on bleeding vessels. In spite of the presence of a very large neoplasm and obvious handicaps due to previous surgery, this tumor was removed without difficulty through a thoracoabdominal approach. This is the first recorded case of the thoracoabdominal removal of a renal tumor of which I am aware.

Mortensen proposed three main principles to be followed in the surgical attack on renal neoplasms: the removal of the perirenal tissues with the kidney; early ligation of the renal pedicle; and avoidance of unnecessary trauma to the tumor to prevent forcing tumor cells into the veins.

These sound principles seem to be adequately met by the thoracoabdominal approach. Since the five-year cure rate for malignant tumors of the renal parenchyma probably has averaged 20 per cent or less,[11] a more effective method

of dealing with these neoplasms is welcome. In 1948 Chute and Soutter[12] described the technic of thoracoabdominal nephrectomy as applied to 5 cases of renal neoplasms, and Chute, Soutter and Kerr[13] reported on the same subject at the May 16, 1949, meeting of the American Urological Association in Los Angeles. They reported 39 thoracoabdominal operations, 20 of which were for renal neoplasms.

By the thoracoabdominal approach it has been possible to remove large renal neoplasms more effectively and with more safety than by previous methods. Furthermore, certain tumors that had previously been unsuccessfully attacked through lumbar or transperitoneal incisions have been removed successfully by this approach. In addition to renal neoplasms, the thoracoabdominal route has been employed for the removal of kidneys badly diseased from chronic pyelonephritis or calculous disease. Tuberculous kidneys, which had been considered impossible to remove because of marked deformities of the spine, have been removed successfully by the thoracoabdominal operation.

The removal of a diseased kidney through the chest necessitates a training in thoracic surgery or a thoracic surgeon and a urologist working together as an operating team. Many renal lesions will continue to be treated best by former surgical procedures, but the thoracoabdominal operation has a definite place in the surgery of the diseased kidney, particularly in the removal of large renal neoplasms. During the past year and a half, 43 thoracoabdominal operations for renal lesions were performed at the Massachusetts General Hospital, the majority being for suspected renal neoplasms. Complications following this procedure have been few, and the mortality has been low.

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Correction. In the Medical Progress report "Rh and Other Blood Groups" by Drs. Louis K. Diamond and Fred H. Allen, Jr., which appeared in the December 1 issue of the *Journal*, the following corrections should be made in Table 4: in the first column the subgroup "rh′ rh‴" should read "rh′ rh‴″"; the subheading of the seventh column "(anti-Rh'_0)" should read "(anti-Rh_0)"; and the subheading of the last column "(anti-Hr′)" should read "(anti-Hr″)."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36031

PRESENTATION OF CASE

A sixty-six-year-old Irish-born American widow was admitted to the hospital with swelling of the neck and generalized weakness.

She had been in good health until one year before admission, when she first noted a small, nontender, midline swelling beneath her jaw, associated with slight enlargement of her tongue and loosening of her lower front teeth. At approximately the same time she became quite nervous and experienced nausea with vague abdominal distress. Hospitalization elsewhere for a period of three weeks yielded no diagnosis but the patient was discharged improved. Nine months prior to admission she suffered a sudden attack of severe dyspnea associated with a choking sensation in her neck. She was rehospitalized and received oxygen and digitalis, with noteworthy improvement. A diagnosis of coronary occlusion was made, and she was discharged on digitalis to a convalescent home after three weeks. For seven months preceding the present admission the patient noted steady increase in the neck swelling and enlargement of her tongue. She developed some difficulty in swallowing but was able to ingest all types of food if she ate her meals very slowly. The lesion was painless and unassociated with hemoptysis or hematemesis. There was a weight loss of 25 pounds during the year preceding admission.

Physical examination revealed an underweight woman in no distress. A midline, nontender mass was palpable in the neck, under the jaw, extending from one mandibular angle to the other (Fig. 1B). The lesion was unattached to the skin, freely mobile and moved upward on swallowing. It was firm centrally but soft and irregular laterally. It could not be transilluminated, and no bruit was heard over it. Some observers felt the lesion to be a part of or attached to the base of the tongue; to others, it imparted a cystic or "wormy" outline. The tongue was markedly enlarged but otherwise normal (Fig. 1A). The thyroid gland was not palpable. The heart was somewhat enlarged to the left, with a Grade II, rough, systolic murmur at the apex. There were slight dullness to percussion, and decreased breath sounds and voice sounds at the right-lung base. The abdominal examination was not remarkable.

A B

FIGURE 1.

The temperature was 99°F., the pulse 86, and the respirations 20. The blood pressure was 120 systolic, 90 diastolic.

The urine had a specific gravity of from 1.010 to 1.015, gave a ++ test for albumin, and the sediment contained many pus cells. The hemoglobin was 11.7 gm., and the white-cell count 11,500, with 52 per cent neutrophils, 40 per cent lymphocytes and 8 per cent monocytes. The nonprotein nitrogen was 25 mg., the alkaline phosphatase 3.7 units, and the total protein 7.08 gm. per 100 cc., with 3.23 gm. per 100 cc. of albumin and 3.85 gm. of

globulin. The basal metabolic rate was —2 and —14 per cent. A blood Hinton test was negative. Chest x-ray study showed generalized cardiac enlargement shared by the left auricle, left ventricle and right ventricle. The right costophrenic angle was obliterated, and there was marked thickening of the pleura over the right lung. Fine linear and nodular densities consistent with emphysema and fibrosis were present in both lung fields. A barium swallow showed no deviation in the neck. Three small areas of decreased density in the vault of the skull were consistent with metastatic tumor or localized atrophy. No bony abnormalities were recognized in the jaw, and the remainder of the skeletal survey was noncontributory.

The patient had moderate difficulty in eating because of the enlargement of her tongue. She suffered moderate shortness of breath and orthopnea. There was no pain, and the cervical mass did not change in character.

An operation was performed on the eighth hospital day.

Differential Diagnosis

Dr. Claude E. Welch*: Are there any x-rays?

Dr. Stanley M. Wyman: No.

Dr. Welch: I had hoped that I might get Dr. Wyman up and worm a little more information out of him than I was able to get from reading the report since I cannot make anything definite out of the reported "spots in the skull" and we would like some definite fact from which we could precede with the case. As it stands, we are faced with a problem of a lump in the neck of an elderly woman, who had noted it for one year. Since it had appeared, the teeth had fallen out and she had become weak and lost weight. Theoretically, it should be easy to run down the possibilities of such a mass in the neck. But if any of you have tried it with a group of medical students, you will know that in a group of eight students, eight diagnoses of a mass in the neck will be made and no one will be right. Let us try to make a diagnosis, nevertheless.

In the first place, we ought to try to decide whether the mass was inflammatory or whether it was tumor; we have no real evidence that it was inflammatory. We would have to consider syphilis, but the blood Hinton reaction was negative and furthermore one would expect the course to have been different if syphilis had been present. Tuberculosis is another common lesion in that area. Again, we have no reason to expect it. Quite conceivably, there would have been some calcification in the mass if that had been the situation. I think, therefore, we are not dealing with inflammation but with a tumor.

*Associate visiting surgeon, Massachusetts General Hospital.

What kind of tumor? To be a little more specific, if it were a benign tumor in this locality, I would consider the possibility of a cyst, probably thyroglossal in origin. Of course a thyroglossal cyst, noted at this age, is unusual, and even though some observers thought the mass to be cystic it may not have been. As all of you know, when a mass appears in the midline in the neck there is often a large amount of edema associated with it — the typical neck of a turkey gobbler appears from the presence of the mass itself, whether it is benign or malignant. Are there any other benign tumors that ought to be considered? When we think of the wormy sensation that some people outlined, we think of the possibility of hemangioma or, less commonly, of lymphangioma, and also of neurofibroma. Grouping these together we really have little else to do than list them because it would be uncommon to observe them for the first time in a person of this age. Lymphangiomas, while they occur in this locality in younger patients, are more commonly situated on one side than in the midline. I do not believe that this patient had a benign tumor.

Then we have a little evidence perhaps that the tumor was malignant because she had lost weight and had felt rather weak. Of course, the loss of her teeth could have been enough to account for the loss of 25 pounds, but the rather sudden appearance of the tumor makes the diagnosis of malignant tumor a little more probable.

If it was a malignant tumor, what possibilities do we have? In the neck, of course, one must consider metastatic epidermoid carcinoma from an unknown source — by far the most likely possibility in this location. It would probably be from the base of the tongue or the tongue itself. I would be surprised to find a lesion as large as this due to carcinoma with these physical characteristics. If this were an epidermoid carcinoma, I would expect it to be well fixed. This mass was movable. It would also help if the primary site was found; none could be. Consequently, of the commonest malignant tumors in this locality, I think I will eliminate metastatic carcinoma from the tongue or the floor of the mouth.

Of the other tumors, we should consider metastatic carcinoma of the thyroid gland, and this mass could have been perfectly consistent with that. We also think of lymphoma, which could produce an unusually freely movable mass of this type. We have no other evidence to go along with lymphoma in the way of enlarged lymph nodes, so I believe I will eliminate that. If we consider tumors that involve the skull, we should list carcinoma of the thyroid gland, multiple myeloma, carcinoma of the breast and, very rarely, carcinoma of the stomach or of the kidney. Of that group we have nothing to implicate the breast, kidney or stomach. Multiple myeloma, while not excluded by the normal protein, — the Bence-Jones test is not

mentioned but I assume that if done it was negative, — would be unlikely to produce lesions in the skull and one large mass in the neck.

We come down to what I think would be the most likely possibility but what I admit again would be a "long shot" because there was no palpable thyroid gland in the neck, and that is carcinoma developing in a sublingual thyroid gland with metastases to the skull. I am prepared to be completely wrong.

DR. TRACY B. MALLORY: Are there any questions or suggestions?

DR. JOHN B. STANBURY: Does Dr. Welch consider it worth while to consider the possibility of primary amyloidosis? The patient had an enlarged tongue, with thyroid involvement; this mass could have been the thyroid gland.

DR. WELCH: That is an interesting suggestion. Amyloid disease in the thyroid gland is extremely rare. How many cases have we had? I believe Dr. Kranes made that diagnosis in 1 case.

DR. MALLORY: We have had 3 or 4.

DR. WELCH: Thank you for mentioning it.

DR. EDWARD B. BENEDICT: How do you rule out cancer of the tongue so easily?

DR. WELCH: I do not rule it out easily. But this mass was not quite consistent with a metastatic lymph node from cancer of the tongue, which should have been fixed and definitely hard. Some observers called this mass cystic and wormy.

DR. WYMAN: What value do you put on the statement that it "moved upward on swallowing"? Does that mean anything?

DR. WELCH: No, except that it was attached to the hyoid bone, which would rise on swallowing.

A PHYSICIAN: Do you expect bone-forming metastases with carcinoma of the thyroid gland? Are they not usually osteolytic?

DR. MALLORY: Yes.

A PHYSICIAN: Would you consider thyroiditis? Did she have a Hashimoto or Riedel struma to cause such a picture?

DR. WELCH: The hardest thing is to believe that this was the thyroid gland. It was an unusual location, and I think that is where we are most likely to go wrong. If it was a thyroid gland with a Riedel struma in this location, I think it would be extremely rare and extremely unlikely.

DR. REED HARWOOD: Would not any malignant mass in that region be fixed whether it was lymphoma or carcinoma?

DR. WELCH: Lymphoma would not necessarily be fixed. Metastases from the thyroid gland are often quite freely movable for a long time.

I can see that everyone has a different diagnosis!

CLINICAL DIAGNOSIS

Cystic hygroma of neck.

DR. WELCH'S DIAGNOSIS

Carcinoma of sublingual thyroid gland.

ANATOMICAL DIAGNOSES

Amyloid infiltration of tongue, salivary glands and cervical lymph nodes.
Probable plasma-cell myeloma.

PATHOLOGICAL DISCUSSION

DR. MALLORY: On the wards the examiners were apparently very impressed with the belief that this mass was cystic, and the patient was operated on with a preoperative diagnosis of cystic hygroma of the neck. At operation that was not found. A mass of tissue consisting mostly of salivary gland and a few lymph nodes was taken out along with a biopsy from the base of the tongue, and all the specimens showed infiltration with amyloid.

Subsequent efforts were made to study the case further, and a Congo-red test was done, but 75 per cent of the dye remained in the serum, so that the test was negative. A bone-marrow biopsy was taken in which our laboratory could find no evidence of myeloma but on bone-marrow aspirations of another bone — 2 were done — 1 showed 5 per cent, and the other, 12 per cent of plasma cells. If the latter figure is correct, I think the case was probably one of primary myeloma with secondary amyloidosis.

DR. ANDRIES QUERIDO: I think it is interesting to hear again that the Congo-red test was negative in amyloid.

DR. MALLORY: The terminology of amyloid disease is very confusing. The usual form that is associated with chronic infectious disease is called "secondary." This tends to be a diffuse involvement of many organs occurring in a rather standard pattern including almost always spleen, liver, kidneys and adrenal glands. This type of amyloid usually stains brown with iodine, metachromatically with methyl violet and red with Congo red. "Primary" amyloid disease, in contrast, usually is not associated with sepsis, its deposit is haphazard, often in tumor-like masses, and its staining reactions are very irregular. The type of amyloidosis that is secondary to myeloma is almost always of this so-called primary type.

DR. STANBURY: It might be interesting to speculate about the heart disease, because primary amyloid disease does involve the heart.

DR. MALLORY: Yes.

CASE 36032

PRESENTATION OF CASE

A one-and-a-half-day-old female infant was admitted to the hospital because of fever, vomiting, cyanosis and anuria since birth.

The patient was delivered thirty hours prior to admission after six hours of uneventful labor and without the use of instruments. The membranes ruptured twelve hours before delivery, with a normal amount of amniotic fluid. The primiparous mother had been given scopolamine, Demerol, Nembutal and ether anesthesia for what was described as an uneventful delivery. The color of the baby was reported as poor at the time of delivery, requiring aspiration of mucus and meconium, but she was resuscitated and placed in oxygen. The mother was reported to have had a difficult pregnancy, with blood pressures ranging from 150 systolic, 100 diastolic, to 180 systolic, 120 diastolic, just prior to labor. She had persistent albuminuria and complained of several upper respiratory infections during the pregnancy. She weighed 300 pounds at the time of delivery. A few hours after delivery the patient was found to have a temperature of 106°F. Penicillin therapy was begun, and 50 cc. of saline solution was given by clysis. The infant had passed no urine since birth, had vomited everything offered by mouth and had had no convulsions. Two meconium stools were passed.

Physical examination revealed a rather blue, dehydrated infant, with a weak, high-pitched cry, who was obviously acutely ill. Examination of the head and chest was not remarkable. No blood pressure was obtained. The abdomen was soft and apparently nontender, with no palpable masses or organs. A nasal catheter passed easily into the stomach.

The temperature was 103°F., the pulse 140, and the respirations 50.

The white-cell count was 30,000, later rising to 40,000, with 68 per cent neutrophils. The red-cell count was 5,000,000, with a hemoglobin of 15 gm. Lumbar puncture yielded pink fluid containing 50,000 fresh erythrocytes per cubic millimeter, with only a few lymphocytes. The supernatant fluid was xanthochromic, and the protein content was 630 mg. per 100 cc. Organisms were not demonstrated with a gram-stained smear. A subdural tap yielded clear fluid from the left side and pink fluid with 15,000 red blood cells per cubic millimeter and xanthochromic supernatant fluid from the right side, with a total protein of 630 mg. per 100 cc. X-ray films of the chest and abdomen were reported to be normal. The kidney shadows were not visible; an intravenous pyelogram on the second hospital day showed no dye and also failed to outline the kidneys. The blood nonprotein nitrogen was initially 120 mg. per 100 cc. but rose gradually to 220 mg. on the last day. The calcium was 8.4 mg., and the phosphorus 3.7 mg. per 100 cc.

Penicillin and sulfadiazine were begun on admission, but as soon as the anuria and elevated nonprotein nitrogen were recognized the sulfadiazine, after two doses, was discontinued. The bladder could not be palpated through the abdomen or by rectal examination. With difficulty, the patient was catheterized and cystoscoped, without the demonstration of any anatomical abnormality. There was no urine in the bladder. On the first hospital day the patient was noted to be twitching, with irregular pulse and respirations and a poor color; 0.5 gm. of calcium levulinate was given intravenously without benefit. Intermittent convulsions continued. The course was febrile. The patient was given intravenous fluids (approximately 270 cc. a day) in order to prevent dehydration and provide water for urinary excretion. It was finally decided to explore a kidney. This was done on the fourth hospital day through a right lumbar incision. A normal-appearing kidney was seen; there were double ureters of normal size, one of which was opened and easily probed up into the pelvis and down into the bladder without yielding any urine. Postoperatively the patient's course was unchanged. During the first four hospital days she received sufficient fluids intravenously to cover her insensible water loss; during the last two days the fluids were calculated as for a child who was voiding normally. She died on the sixth hospital day, never having passed any urine since birth. A blood culture was negative.

Differential Diagnosis

Dr. Stewart H. Clifford*: This infant had vomiting, cyanosis, anuria and a high temperature from birth and was in desperate condition on admission to the hospital. The history of the mother's pregnancy was abnormal. We have a primiparous mother with severe toxemia, albuminuria and an elevated blood pressure; she weighed 300 pounds at the time of delivery. We would naturally like to know whether this was a sudden weight gain related to her pregnancy. What was her weight at the beginning of the pregnancy? I think one can assume that a portion of that weight was excess fluid. We must decide whether the baby's dramatic symptoms were the result of intrauterine disease, of factors acting during birth or of changes occurring after birth. With the symptoms present at birth in addition to the story of the mother's pregnancy, one suspects that the problem began a long time before actual birth. We do not know whether the baby was born at term, prematurely or postmaturely.

A Physician: She was a full-term child.

Dr. Clifford: Do you know the birth weight?

A Physician: Six pounds, nine ounces.

Dr. Clifford: This infant may have been influenced by toxemia in utero, through involvement of the placenta. The mother may have had a grossly infarcted placenta, inefficient as a means of eliminating the waste from the baby and in providing oxygen for the baby. It would be interest-

*Consultant to Children's Medical Service, Massachusetts General Hospital.

ing if we had further information about the placenta. We now know that the infant was full-term and weighed over 6 pounds. Was the placenta normal?

A PHYSICIAN: I do not remember.

DR. CLIFFORD: There may well have been interference with the baby's intrauterine development as the result of a diseased placenta. When a fetus must live off a diseased placenta, there follows a reduction in its oxygen supply that may result in a seriously damaged infant at birth. However, the history to this point gives us no basis for suspecting intrauterine anoxia.

DR. ALLAN M. BUTLER: The baby's condition at the time of delivery required aspiration of mucus and meconium.

DR. CLIFFORD: The need for resuscitation can be the result of factors operating during delivery, as well as from intrauterine anoxia. We have no evidence of any long-continued anoxic process; this was probably an acute process. This full-term baby was malnourished; many of the babies of toxemic mothers are below expected weight because of the impaired placental circulation.

The next speculation might be whether there was anything such as a congenital defect that might explain the baby's predicament. We hopefully turn to the physical examination for a clue. What caused the cyanosis at birth? Was it a congenital heart abnormality? We have no evidence of such a condition. The x-ray studies were normal, and no murmur was described. On the other hand, certain congenital anomalies of the heart, such as a two-chambered or three-chambered heart or a transposition of the great vessels, may cause no murmur or cardiac enlargement. On the information we have been given I cannot make the diagnosis of a congenital heart lesion.

During delivery the baby must have had severe anoxia as evidenced by the aspiration of meconium. Atelectasis resulting from anoxia could give this clinical picture. However, the physical examination of the chest was negative. The x-ray examination did not show atelectasis sufficient to account for this clinical picture. The anoxia during birth, although sufficient to produce aspiration of meconium, was not enough to produce the picture of this cyanotic baby.

What else have we to consider? Intracranial hemorrhage will produce a severely cyanotic baby at birth; but there was no evidence of traumatic injury. The mother delivered normally as far as traumatic factors are concerned. We have a history of sufficient anoxia to have produced a minor amount of hemorrhage into the subarachnoid space; I suspect that there was slight intracranial hemorrhage, but I am very reluctant to explain the whole process by that diagnosis.

What else could have caused this picture? Anoxemia in the new-born infant can produce adrenal hemorrhage. Adrenal hemorrhage is even more common in the combination of anoxia and breech delivery. The cyanosis, the vomiting and the anuria, — presumably the result of shock and dehydration, — as well as this extremely high temperature of 106°F. within a few hours of birth, are suggestive of the so-called Waterhouse–Friderichsen syndrome associated with a lesion of the adrenal gland. We should keep that in mind definitely as we go down the examination.

Vomiting soon after birth makes one think of some congenital anomaly. Under these circumstances one has to rule out tracheoesophageal fistula. That is the reason the catheter was passed into the stomach. That, in addition to the x-ray studies, makes me eliminate this type of congenital anomaly. Another consideration is whether the baby had malrotation and obstruction of the second portion of the duodenum, in which case x-ray examination would have shown a dilated stomach and first portion of the duodenum, with the rest of the abdomen free of air. The plain film of the abdomen showed no evidence of a congenital anomaly of the gastrointestinal tract to explain the vomiting.

The lumbar puncture does give the anticipated evidence of intracranial bleeding of the type associated with asphyxia. Traumatic injury with rupture of a tributary or larger vein could have produced gross blood. The xanthochromic supernatant spinal fluid with a protein of 630 mg. per 100 cc. is evidence of hemorrhage and blood destruction. To make sure the infant did not also have a subdural hematoma, the subdural region was tapped and identical fluid was obtained, demonstrating a communication between the lumbar and the cerebral subarachnoid space. There was no localized subdural hematoma. We can conclude that the baby did have intracranial hemorrhage of the anoxic type but probably not enough to account for all the clinical findings.

The anuria is the real problem in this case. The baby came in, at the age of thirty hours, and had not voided. She was dehydrated. Babies frequently do not void, even normal babies, for forty-eight hours. Any baby, particularly a dehydrated one, can go thirty hours without voiding and not cause any particular concern. This patient's nonprotein nitrogen progressively increased. An infant's nonprotein nitrogen during a period of starvation, such as this child had, could easily be 120 mg. per 100 cc. with normal kidneys, and the continued starvation and wasting of body tissues, with failure to eliminate any fluid from the kidneys, could account for the further increase noted in the nonprotein nitrogen. One wonders whether the sudden shutdown of the kidneys was due to an infectious process. The penicillin and sulfadiazine were probably given on the assumption that the baby had an infection although no positive evidence of infection was found. We have the history that the mother had repeated infection during her preg-

nancy, and one could speculate whether or not she had been given sulfadiazine that sensitized the baby to the drug. This is so remote a possibility that it cannot be considered seriously.

We have to decide whether a congenital anomaly could explain the anuria. The bladder and urethra were normal. The double ureters discovered at operation could not have caused the infant's difficulty. The intravenous pyelogram revealed that the kidneys were not functioning — the dye did not pass from the blood through the kidneys. That makes one wonder whether a congenital anomaly, such as polycystic kidney, could have been present. Polycystic kidneys that one sees at this age are not necessarily enlarged, but I have never seen a polycystic kidney produce complete anuria; there is usually some urine secretion, and the possibility of polycystic kidney as an explanation for this complete anuria is very difficult to accept.

The convulsions, of course, are easily explicable on the basis of both anuria and intracranial hemorrhage. It is not unusual for the baby of a severely toxemic mother to have intrauterine anoxia with multiple hemorrhages. This could have involved the adrenal glands, to produce a Waterhouse–Friderichsen syndrome at birth. The baby had intracranial hemorrhages. The anuria I am forced to explain on a physiologic basis, the chief cause being the dehydration of the infant. I would be very much surprised if we found a congenital anomaly.

One more point that this baby brings up is whether it is possible for toxemia and a kidney lesion in the mother to be transferred to the fetus and for the baby to have an eclamptic type of kidney lesion. A few cases have been reported in which the baby's kidney was involved with the mother's process. I have never seen one.

Dr. Nathan B. Talbot: I suppose the sections of the kidney will show uric acid crystals.

Dr. Clifford: I have no doubt of that.

Dr. Talbot: Do you think it is inconceivable that such uric acid infarcts, so called, could prevent urine flow?

Dr. Clifford: I would expect the baby to have kidneys loaded with crystals as many dehydrated babies have. But, again, all the evidence in the literature is that this is secondary and cannot explain the anuria. I should think it was part of the physiologic picture and not the cause of the anuria. It is hard to conceive how uric acid infarction could cause complete anuria from birth. With this picture of dehydration, I would not be surprised to find thromboses in many veins.

Dr. Benjamin Castleman: Would you make a diagnosis of Waterhouse–Friderichsen syndrome in the absence of infection?

Dr. Clifford: In the newborn infant anoxia does produce adrenal hemorrhage in the absence of infection.

Dr. Castleman: Just anoxia in the absence of infection?

Dr. Clifford: Yes.

Dr. Fletcher H. Colby: It might be a help to know certain things that were not brought out clearly. To me, the baby looked fairly well during the first forty-eight hours. At the time of cystoscopy she was not dehydrated, the skin was not dry, and she seemed to be in reasonably good general condition in spite of the high nonprotein nitrogen and uremia. She obviously never had any urine in her bladder. A baby's bladder, at birth, extends 3 or 4 cm. above the symphysis and is essentially an intra-abdominal organ, not a pelvic organ. This baby's bladder was small and contracted and gave the impression that it was never physiologically active at any period. We thought this problem over a great deal and had no idea what was wrong. At the time of operation the skin and subcutaneous tissues were slightly edematous. The perirenal fat was of normal amount and of normal consistence, not edematous, and the kidney itself was perfectly normal. The configuration of the ureters was normal except for a double ureter and a normal renal pelvis. When the renal pelvis was opened no urine was present within the kidney.

Another significant fact is that the pulsation of the renal artery felt and appeared like that of a perfectly normal renal artery. Those were the facts we had to go on. If we had been dealing with an adult we might have come nearer making the correct diagnosis. This was a normal-appearing kidney, with a normal collecting portion and normal arterial supply. The bleeding from the kidney at operation was red arterial blood, yet the kidney was not putting out urine. In an adult that is usually due to a lesion of the renal blood supply. If the renal arterial supply is normal, as we had every reason to suspect it was here, then we should have been suspicious of the venous return of both kidneys.

Dr. Clifford: In venous thrombosis, would you not expect hemorrhage?

Dr. Colby: Not necessarily.

Clinical Diagnosis

Agenesis of kidneys.

Dr. Clifford's Diagnoses

Intracranial hemorrhage, anoxic type.
Adrenal hemorrhage.
Dehydration.

Anatomical Diagnoses

Renal-vein thrombosis in newborn infant.
Cerebral hemorrhage with rupture into ventricles.

Pathological Discussion

Dr. Castleman: The bladder was slightly swollen and trabeculated, but not too abnormal. Grossly,

the kidney that was operated upon showed one hemorrhagic area in the pyramids of the lower pole. The left kidney, on the other hand, had many hemorrhagic spots throughout the entire kidney. The left renal vein was thrombosed, the thrombosis extending to the inferior vena cava but not into it; the right renal vein was not thrombosed. Microscopical examination of the kidneys showed numerous thromboses of the intrarenal veins in both kidneys. This apparently produced extensive hemorrhages of the pyramids without any real necrosis of the renal parenchyma. One might call it renal venous infarction. Had the child lived longer there would have been destruction of the kidney tissue, rather than mere outpouring of red cells in the interstitial tissues as was present. This is the first case of renal-vein thrombosis we have had for a long time — a condition not too uncommon in children, especially the newborn infant. One of the earliest papers on this subject was a monograph written in 1877 by Hutinel,[1] a Frenchman, who collected 42 cases of renal-vein thrombosis in children under one year of age. Most of them were in the newborn infant, and in 30 cases, the lesion was bilateral. The etiology of this condition is still unknown, but it is believed that dehydration and venous stasis, rather than infection are the more important factors. Cases have been reported in which the thrombosis is present only in the main renal vein or only in the smaller intrarenal veins, or in both. In a few cases there has been thrombosis in other organs as well, but these are exceptions. In the case under discussion the fact that both kidneys had renal-vein thrombosis within the kidney and that in only one had the thrombosis extended into the main renal vein probably means that the process started as an intrarenal disease.

DR. BUTLER: Was there any disease in the adrenal glands?

DR. CASTLEMAN: They were normal.

DR. CLIFFORD: What was the age of the thrombus?

DR. CASTLEMAN: Some of the thrombi showed early organization. The main renal thrombus was adherent to the renal vein and I think it occurred before birth.

DR. W. MCK. JEFFERIES: What was the mechanism of the anuria?

DR. CASTLEMAN: In going over the reported cases[2, 3] of renal-vein thrombosis in infants, I noticed reports of some oliguria but no case with anuria. This is the only patient we were able to find who had anuria. This is not true in the adult, in whom anuria is a prominent symptom.

DR. EARLE M. CHAPMAN: Did anuria contribute to the thrombosis?

DR. CASTLEMAN: I do not know. It would be hard to say whether the thrombosis was six or eight days old — that is, whether it appeared during or just before labor. I do not believe, however, that it occurred long before that.

DR. COLBY: The kidneys were normal in size and I believe were working until either just before labor or just after it.

DR. CHARLES S. KUBIK: There was hemorrhage into one of the caudate nuclei. This had ruptured through the ependyma of the ventricle, filling all the lateral ventricles with blood, and there were a number of small foci that looked like hemorrhagic infarcts, with slight softening of the tissue but without any apparent hemorrhage.

DR. BUTLER: The hemorrhage may have occurred very late.

DR. KUBIK: Yes. It was not very old. There had been bleeding because there was xanthochromic fluid.

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ANTIHISTAMINIC COLD CURES AND MODERN SALES METHODS

SEVERAL times each day radio listeners are asked to go to their drugstores to purchase good supplies of the new antihistaminic preparations, and they are urged to insist on the particular brand that is being advertised. All these antihistaminic preparations are described as completely effective, entirely safe and free from all harm and dangers. The listeners are told that these drugs are practically certain to *prevent and to cure* promptly the common cold and all its discomforts. Similar advertisements appear in the daily newspapers either in full-page spreads or in lay-outs of only slightly more modest proportions. Several such advertisements by different manufacturers or distributors often appear in the same issue of the daily paper. In each of these radio commercials or newspaper advertisements, the listener or reader is told to read the December issue of the *Reader's Digest* for the proof of their claims.

The article referred to begins very auspiciously by stating that "November 15, 1949 marked the beginning of a great step ahead in the comfort of mankind." "On that day," the writer goes on to say, "occurred the scientific publication in the *New York State Journal of Medicine* of a powerful and a practical preventive and cure for the common cold." The rest of the article cites names and places and emphasizes the complete safety of the new antihistaminic drugs and the certainty with which they prevent and cure the common cold. Particular emphasis is placed on the fact that these agents can be purchased over the counter without prescriptions.

Should any reader be rash enough to question the authority of the writer or should he wish to go to the source referred to in the *Reader's Digest* article, he would be sorely disappointed to find not a word of reference to either the names or the subject matter of this article in the issue so auspiciously announced. Physicians who look for this article likewise will fail to find any reference in the *New York State Journal of Medicine* of November 15. If, however, they are among the rare persons who do not immediately relegate each day's advertising mail to the waste basket and if they take the trouble to open each item and to scan the subject matter, they will have found, among the pre-Christmas deluge of advertising matter from the various drug houses, one that contained a letter from the office of the president of a large corporation referring to an enclosed reprint as containing the "clinical evidence." A perusal of this reprint will at once recall the names and the details referred to in the *Reader's Digest*. The article,[1] which deals with the antihistaminic agent in which this company is particularly interested, was reprinted (or preprinted) from the December, 1949, issue of an entirely different journal.*

The validity of the claims for the antihistaminic drugs as cold cures has been criticized in a brief comment that appears in the December 10, 1949,

*Incidentally, data of a clinical trial of the same agent in the treatment of cases of "vasomotor rhinitis" and "hay fever," published seventeen months earlier, indicated that the drug was relatively effective and of low toxicity.[2]

issue of the *Journal of the American Medical Association*. In this note it is stated that the Council on Pharmacy and Chemistry at a recent meeting warned against the indiscriminate use of the antihistaminic substances, which are now being promoted for the prevention of colds or even for the treatment of those suffering from colds. The Council, in contrast to the *Reader's Digest's* authority, is not convinced that the data are sufficient to warrant the positive statements and claims that are being made. The Council further warns that cases have been reported in which users of these drugs became drowsy and even fell asleep while at work and, occasionally, while driving cars or operating machinery. The Council also believes that experience with these substances is still insufficient to determine whether they are harmless when used over long periods and indicates that the amounts taken in persistent colds may exceed what has been established as normally safe.

Whatever the merits of antihistaminic agents may prove to be, the methods used in advertising and promoting the sales of these substances are certainly to be decried. Although these "plugs" may not be quite as revolting to radio listeners as some of the commercials addressed to young women with menstrual discomforts they represent unfortunate exaggeration and distortion over which there is at present no effective control. Furthermore, this is the most striking example to date of the advertising methods of manufacturers and promoters who are steadily going over the heads of the members of the medical profession in attempts essentially to force physicians through their trumped-up public demand to accept remedies before their usefulness has been adequately substantiated and ill effects determined by the usual slow but more thorough and critical methods of clinical investigation.

The medical profession and indeed all thoughtful persons interested in the health and welfare of the people have good reason to be shocked at this type of medical advertising direct to the public. Meanwhile, the promoters of these methods are gloating over the rapid results *they* are getting, and they count their returns in the millions.

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HAZARDS OF DIAGNOSTIC PROCEDURES IN INFECTIOUS DISEASES

In a recent article in the *Journal*, Sulkin and Pike[1] reviewed the subject of viral infections contracted in the laboratory. They summarized 222 laboratory infections due to viruses; 21 of them were fatal. The probable sources of these infections in at least a third of the patients was the handling of animal tissues; 30 patients were presumed to have been exposed to a contaminated atmosphere, 13 had handled infectious material from patients, and 19 had worked with material from infected chick embryos. Known accidents were responsible for only 27 of the cases; the most common situation involved the splashing of infectious material in the face or eyes. It was pointed out that the first recognized cases of human infection with viruses of louping ill and Newcastle's disease were contracted in the laboratory.

Probably more frequent than the viruses as sources of human laboratory infections are infections with rickettsial agents. The typhus fevers are well known in this regard, and few indeed are the laboratory workers who have carried out extensive studies involving the handling of rickettsial infected materials who have not themselves contracted infections with these agents. The most recent of the rickettsias that well emphasizes the hazards of the laboratory as a source of infections is *Coxiella burneti*, the agent of Q fever. In this instance, too, the first recognized human infection and the first outbreak of Q fever in this country were laboratory infections.[2]

Reference to laboratory infections with organisms other than viruses and rickettsias was also made in the review by Sulkin and Pike. These include brucellosis, tularemia, plague, anthrax, typhoid fever, glanders, relapsing fever, leptospirosis, syphilis, tuberculosis and a host of others. Even pneumococcal pneumonias have been acquired from the labora-

tory manipulation of sputum,[3] and occasionally pneumonia acquired in this way by laboratory technicians has proved fatal.

In this tissue of the *Journal* Looney and Stein call attention to the serious hazard affecting primarily workers in hospital laboratories who handle pathogenic materials from cases of coccidioidomycosis. This is all the more important a hazard in regions like New England, where the disease is extremely rare and where neither the physician nor the laboratory worker has an opportunity to become familiar with the disease and with the causative agent. Even well informed physicians and well trained technicians may not be fully aware of the precautions required to prevent such infections, if indeed that is possible. The authors have reviewed all the previously reported cases of laboratory infections with *Coccidioides immitis*. They include 8 cases proved by the isolation and identification of the organism and a large number of clinical cases in which positive skin reactions to coccidioidin developed. There was 1 death among the laboratory-proved cases.

The great hazard involved in attempts to grow and identify the organism is emphasized by these writers. This hazard extends not only to the workers directly concerned but also to those who may be working in the same laboratory, in other parts of the same building and even to innocent persons who may merely be passing by or visiting in the laboratory. Even Dr. Charles E. Smith, of San Francisco, who has probably had more experience with this organism and with the clinical disease than any other person, has given up the use of certain types of cultures on solid mediums because of the number of infections acquired from the handling of such cultures. Looney and Stein have brought out the fact that person-to-person transmission of coccidioidomycosis or even the transfer of this disease from infected animals to human beings does not occur, or is extremely rare, although either of these modes of infection seems possible.

These reports of laboratory infection should impress upon clinicians the importance of giving consideration to the health and welfare of the laboratory workers who are engaged in the handling of infectious material for diagnostic purposes. They should also impress hospital administrators of the need for adequate protection of laboratory personnel against this type of occupational hazard.

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NO COMPROMISE

THE *Boston Herald*, in an editorial published on January 2, has seen clearly and stated convincingly a principle that must appear to the majority of Americans to be a basic truth. Life is unnegotiable. Life cannot be bartered or exchanged or bought or sold or considered in any way except as a sacred and personal responsibility. It can pass in only one direction; once taken it can under no circumstances be restored.

The clergyman and the physician, if they see a common duty clearly, are in agreement on their attitude toward life. "Unless you and I are to revise radically our conception of our common task," according to Dean Willard L. Sperry,* "it is not our business to take life, only to try and save it." Albert Schweitzer, a physician and a clergyman, crystallized his own creed in the words "reverence for life," and as Sperry said, "if we have lost that reverence we have slipped our moral moorings."

Arguments have been presented many times in favor of the taking of human life under strictly guarded conditions, as an act of mercy to a hopeless sufferer. The difference between right and wrong seems then to be but a hairline, but what an inflexible moral barrier that line can become, once it is sharply drawn!

How seldom, as Dean Sperry pointed out, are these moral dilemmas a matter of choosing between black and white, and how often a difficult choice between two shades of gray! And yet, when what seems to be the lighter shade is chosen it must become as pure white.

The world has witnessed a mass loss of reverence for life that has followed what purported to be a

*Sperry, W. L. Moral problems in practice of medicine. *New Eng. J. Med.* **239**:985-990, 1948.

justifiable letting down of the barriers. Such risks should not be lightly taken. For the physician, trained to respect life, that respect should be his first consideration, admitting no compromise, for on it his calling is founded.

ACTIVE-PASSIVE IMMUNIZATION

ELSEWHERE in this issue of the *Journal*, a letter from a Boston surgeon calls attention to the dangers as well as the inconveniences that may result from the use of antitoxin for passive prophylaxis against tetanus. The letter rightly emphasizes both the risk of delayed tetanus in such cases and the complete absence of any permanent benefit to the patient after the effect of the antitoxin has worn off. The correspondent therefore advocates the use of combined active-passive immunization in all such cases, so that a permanent immunity may be superimposed on the transitory protection derived from antitoxin.

This procedure (sometimes referred to as "serovaccination") consists, simply, of the administration of an active immunizing agent (toxoid in this instance) at the same time that antitoxin is given for passive prophylaxis to a patient having no previously established immunity. The procedure has been the subject of vigorous and indeed acrimonious debate for a good many years, the opposition to its use being based on the belief that circulating antitoxin in the patient (in the high concentrations that follow the usual doses of prophylactic antitoxin) will "blanket" any toxoid injected and thus inhibit its action as an antigen. There is some evidence to support this thesis.[1-4]

On the other hand, there is perhaps even more convincing evidence that combined active-passive immunization, when properly employed, will induce a lasting type of immunity not significantly inferior to that induced by administration of toxoid alone.[5-8] Undoubtedly, however, as noted by Downie et al.,[7] "Much of this confusion has resulted from the use of different methods of experimental approach to the problem." Nevertheless, from a study of the various reports on the subject, one may draw certain conclusions suggesting that the conflicting observations cited may be harmonized: Injection of a large dose of antitoxin (for example, 10,000 to 100,000 units) may effectively block the antigenic power of toxoid.[4] Injection of a single dose of toxoid, simultaneously with the usual prophylactic dose of antitoxin, may be ineffective.[2,3] The first of two or more doses of toxoid may induce little or no detectable immune response[8] (this should occasion no surprise, since an initial dose of toxoid produces little immune response even under ideal conditions). The injection of a full course of toxoid may result in adequate immunization[5-8] (the results, when detailed comparisons have been presented, appear to be slightly, but not markedly, inferior to those obtained with toxoid alone.[7,8] Finally, when a comparison was made in animal experiments, alum-precipitated toxoid appeared more effective than fluid toxoid.[8]

Although it is difficult to generalize, one may safely state that "combined active-passive immunization" has become widely accepted, not only in France, where it has long been advocated by Ramon, but also in this country, where it has been officially recommended by the Surgeon General's Office, United States Army, for at least six years.[9,10] Moreover, its use is recommended in a detailed statement by an outstanding British authority on immunization, in a manual prepared as a guide on this subject for general practitioners and medical students.[11]

In view of this general acceptance, it is well to examine the limitations and precautions to be borne in mind in applying this procedure. It is suggested that they would be chiefly as follows: Active-passive immunization or "serovaccination" is, of course, only to be employed in persons who require protection against the disease in question and who are not known to have been previously immunized; for those who have been immunized in recent years, a booster dose of toxoid should ordinarily be sufficient.[12] Serovaccination cannot be depended on to provide active immunity in the face of larger than the usual prophylactic doses of antitoxin. Serovaccination cannot be expected to work more rapidly or with fewer doses of toxoid than in simple active immunization — thus, one cannot safely omit the usual periodic doses of antitoxin in a patient in continuing danger of tetanus,

simply because active immunization has been started. Precipitated toxoid is probably preferable to fluid toxoid for active-passive immunization. Once the procedure is instituted, it must be followed through to completion (the patient who has had antitoxin and one dose of toxoid is liable to consider himself immune unless clearly disabused of this idea, and the occurrence of even one case of tetanus in such a patient whose immunization had been begun but was not completed would be a discredit to the medical profession and to preventive medicine).

Bearing such precautions as these in mind, the medical profession may find active-passive immunization a valuable preventive tool in the practice of medicine.

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An English surgeon, who found his way to California, writes home that he had received thirty ounces of gold, or about $500, for amputating a limb.

Boston M. & S. J., *January 16, 1850*

MASSACHUSETTS MEDICAL SOCIETY

MEETING OF THE COUNCIL

The winter meeting of the Council of the Society will be held at 10:00 a.m. February 1 in the auditorium of the Boston Conservatory of Music on Hemenway Street, in the rear of the Boston Medical Library. *Councilors will please notice change of time and place.*

At this meeting the Council will consider the joint report of the Committee on Fees and the Subcommittee on Blue Cross–Blue Shield Problems, which have been studying the matters of increasing subscription charges, fees, and the income limit for subscribers.

Several other of the Society committees will submit reports. Among them the Committee on Public Relations, at the request of the Norfolk District Medical Society, will recommend the appointment of a subcommittee to study the problem of standard, brief insurance forms. The Subcommittee on National Legislation will report on a letter sent to all senators and representatives from Massachusetts, commenting on several of the health bills now before Congress and suggesting amendments that would make them more in line with advanced medical thought.

The Committee on Publications will recommend the preparation of an extension of Dr. Burrage's history of the Society, bringing it up to date for the 175th anniversary of the Society in 1956. The Committee on Pilot Clinics will report on the successful establishment of the first clinic, which was opened to the public at the New England Center Hospital on January 3. The Committee on Hospital and Professional Relations will report on progress made in its efforts to develop a realistic understanding between the Society and the Massachusetts Hospital Association.

As usual, a complete report of the proceedings will be published in a subsequent issue of the *Journal*.

H. Quimby Gallupe, *Secretary*

NOTES FROM THE MEDICAL EXAMINER*

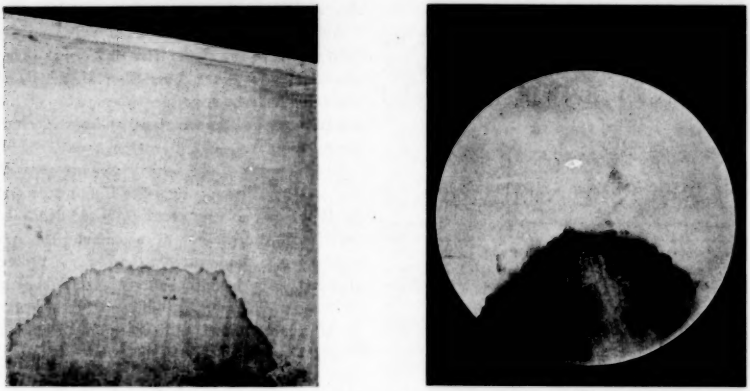
A NEW TEST FOR SEMINAL STAINS

The medicolegal identification of seminal stains in cases of rape is a difficult and frequently unsuccessful process, for it has been customary to base this identification solely on the presence of intact spermatozoa.† It is well recognized that a fairly large proportion of true seminal stains may contain no spermatozoa[2] or that the sperm may be obscured or destroyed by the foreign matter with which they are contaminated. It is of as great importance to recognize such cases as those in which the sperm are abundant. And yet, until recently, there have existed no alternative criteria of high probative value.

With the discovery of the intense acid phosphatase activity of prostatic secretion, new definitive test methods for semen have become available. The use of quantitative determinations of the acid phosphatase activity of extracts of seminal stains was recently reviewed in these notes.[3] It is the purpose of this paper to present a different method of recognizing acid phosphatase activity in seminal stains, based on a histochemical technic of Seligman and Manheimer.[4] The procedure is rapid, and the results graphic. It is particularly suited as a screening test for medicolegal purposes.

The portion of the garment to be tested is immersed in a bath at pH 5 containing alpha-naphthyl phosphate as a substrate, and a suitable diazonium salt. The acid phosphatase of the semen acts on the phosphate ester to liberate alpha-naphthol. This immediately reacts with the diazonium salt to form a brilliant orange-red azo pigment, which is insoluble under the conditions of the test, and which becomes adherent to the background at the site of acid phosphatase activity.‡

The phosphatase activity of a fresh, dry seminal stain is so intense that within thirty seconds a distinctive, visible coloration occurs, and within two minutes the test is complete. When the semen is found to be mixed with blood, as not infrequently occurs in cases of rape, an interesting color change occurs. The blood itself turns to a dirty brownish gray when immersed in the substrate bath. Wherever semen is present, this color is gradually replaced by the orange red of the phosphatase catalyzed pigment. Bloody stains should be developed longer than others, in order that the pigment formed by the semen may be visible above the background.



A B

FIGURE 1. *Photographs Showing* (A) *a Seminal Stain on Handkerchief and* (B) *Print of the Same Stain on Moist Filter Paper, Developed with Seligman-Manheimer Solution.*

*Presented by the Department of Legal Medicine, Harvard Medical School.

†This view has been adopted generally by English and American authorities and is conservatively stated by Glaister,[1] "For medicolegal purposes we hold the view that if spermatozoa or at least one spermatozoon are not found in the stain, we cannot positively affirm that such stains are seminal, and that the apparent absence of these bodies does not permit of an opinion that the stain has not been produced by human seminal fluid."

‡The substrate reagent bath is prepared by dissolution of 23 gm. of sodium chloride, 0.5 cc. of glacial acetic acid and 2 gm. of sodium acetate trihydrate in 90 cc. of water, with the addition of a suspension of 30 mg. of anthraquinone-1-diazonium chloride and 50 mg. calcium-1-naphthyl phosphate in 1 cc. of 1 per cent aerosol. It is well to condition the bath by allowing a known stain to react until the solution takes on a light-red color and some red precipitate forms. An old bath may be used repeatedly by the addition of more substrate and diazonium salt. The original paper of Seligman and Manheimer[4] should be consulted for the preparation of the reagents.

If the suspected stain occurs on an unfavorable background, such as a red wool dress, the red pigment of the developed test is not clearly visible. In this case, and in any case in which it is not desirable to apply the reagents directly to the garment, a portion of the phosphatase of the stain may be transferred to a white filter paper, and its activity detected thereon. It is only necessary to moisten the filter paper, to press it firmly against the area suspected of containing the stain for several minutes and then to immerse the paper in the substrate-reagent bath. Some of the acid phosphatase of the stain on the garment will have diffused into the filter paper sufficiently to cause a print that can be developed. Alternately, a small portion of the material suspected of containing semen may be placed on dry filter paper and moistened with a drop of water. Development of the paper will show a red rosette if semen is present.

Even though the fabric is tested directly with the substrate-reagent mixture, the procedure does not interfere with the subsequent microscopical search for spermatozoa. The seminal fluid takes on a peach-pink color, but the sperm themselves are not colored, for they do not contain sufficient acid phosphatase. If the specimen is then stained with carbol fuchsin, for example, the sperm take on the normal colors produced by that dye. The test thus serves the double function of demonstrating high acid phosphatase activity and at the same time indicating where a search for sperm is likely to be successful. Figure 1 demonstrates that the phosphatase activity is largely concentrated at the periphery of the stain. Sperm are more plentiful in the central area, where they may be demonstrated microscopically.

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JOSEPH T. WALKER, PH.D.

Chemist, Massachusetts Department of Public Safety, and *Associate in Legal Medicine*, Harvard Medical School.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REPORTING OF CONGENITAL DEFORMITIES

It appears that many physicians in Massachusetts are not reporting congenital deformities and other crippling conditions in infants as provided in the law, a copy of which follows:

An Act Providing for the Reporting of Congenital Deformities and Other Crippling Conditions in Infants

[Chap. 326]

SECTION 1. Section three of chapter forty-six of the General Laws, as appearing in the Tercentenary Edition, is hereby amended by adding at the end the following new paragraph:

Within sixty days after the date of the birth of any child born in the commonwealth with visible congenital deformities, or any condition apparently acquired at birth which may lead to crippling, the physician in attendance upon said birth shall prepare upon a form provided by the state department of public health and file with the clerk of the town where such birth occurred a report setting forth such visible congenital deformity, or any condition apparently acquired at birth which may lead to crippling. Said clerk shall transmit forthwith to said department such supplementary report of such birth. The contents of such report shall be solely for the use of said department in connection with its functions relative to crippled children, and such report shall not be open to public inspection or constitute a public record.

SECTION 2. Section twenty-six of said chapter forty-six, as so appearing, is hereby amended by inserting after the word "cents," in the eleventh line, the following new sentence: — For each report of a congenital deformity or other crippling condition transmitted under the last paragraph of section three, a city or town clerk shall receive from the state department of public health a fee of fifty cents, twenty-five cents of which shall be paid by said clerk to the physician making such report.

Approved June 30, 1939.

This amendment became effective on October 1, 1939.

MISCELLANY

MEDICOLEGAL NOTE

The *British Medical Journal* for November 19, 1949, contains an article entitled "Insanity in the Criminal Law of Malta." Crazy laws are found everywhere.

CORRESPONDENCE

PROTECTION AGAINST TETANUS

To the Editor: The protection against tetanus afforded by immunization with tetanus toxoid was clearly demonstrated in the records of wounded and injured in the armed forces in World War II. This protection, it is believed, can be renewed immediately by a single "booster" dose of toxoid. There still remain those, however, who did not serve in the armed forces and who, for any other reason, have not received tetanus toxoid. The threat of serum reactions will still hang over them whenever they are given antitetanic serum. There is an ever-recurring decision to be made regarding prophylaxis against tetanus in fresh wounds.

It has long been recognized, also, that tetanus can develop in cases of long-continued sepsis, as in compound fractures, after the short period of protection from a single dose of antitetanic serum has passed. Administration of one or more injections of antitetanic serum at weekly intervals after the initial injection, as long as sepsis persists, may avoid this complication but will almost inevitably sensitize the patient.

It is suggested, because of an experience in a recent case of delayed tetanus developing several weeks after a severe injury, that every patient not previously immunized, who requires antitetanic serum because of a wound that may remain open for an extended period, be given the first of his immunizing doses of tetanus toxoid at the time of administration of antitetanic serum. Additional injections of the serum may be necessary before his immunity from the toxoid has had time to develop if sepsis is persistent, as in osteomyelitis. At the end of a month, however, the second dose of toxoid may be given, and the patient is thereafter protected from

tetanus without resort to serum. He likewise avoids future reactions from his serum sensitization should later injuries require prophylaxis against tetanus.

In view of the complications always threatening those who have received injections of serum, it is probably not too much to say that any patient who is given antitetanic or other serum for whatever reason should be immunized at that time with tetanus toxoid. The ideal, of course, would be universal protection by the toxoid initiated at the earliest possible age.

GEORGE A. MARKS, M.D.

Winchester, Massachusetts

ACRIBIA, INDEED

To the Editor: The article "Acribia" by Henry J. L. Marriott, in the December 15 issue of the *Journal*, appeared most pertinent to a teacher of medical students. But it was marred by a large and common blemish: the misuse of "regime" for regimen. "Again, the Schemm regime is often. . . ."

Acribia is indeed difficult to achieve.

GEORGE SASLOW, M.D.

Washington University
School of Medicine
Saint Louis, Missouri

Note: A similar criticism was made in a letter to the editor published on September 15, 1949 (P. 430), and a similar reply may serve again. According to *Webster's International Dictionary* (1948), regimen is "1. A governing; government; rule; system; administration. . . . 3. *Med.* A systematic course of diet, etc., to improve or preserve health or attain some effect, as reduction of flesh. . . ."

The abused term regime, however, is defined as "1. Mode or system of rule or management; character of government, or of the social system. . . . 3. *Med.* Regimen." — ED.

BOOK REVIEWS

Science and Imagination in Sir Thomas Browne. By Egon S. Merton. 8°, paper, 156 pp. New York: King's Crown Press, 1949. $2.50.

Not since Thaler's *Sir Thomas Browne and the Elizabethans* has there been such an illuminating and perspicacious appraisal and survey of the science, philosophy and art of the author of *Religio Medici* as this modest but momentous monograph by the distinguished author of *Social Harmonism*. He regards Browne as no mere stylist, but as a scientist, a philosopher and at heart a poet of the foremost rank: "The circumference of Browne's being is represented by his science; the center by his imagination." His learning ranged over the "omne humani scibile" of his time. He was an antiquarian, an eclectic and a virtuoso of science. He had a pure, Hellenic love of truth, and in his quest for it traversed the entire field of knowledge. As a physician his interest was not solely in sick patients but in the nature of disease, of death and of life and in the embryologic origins of life. Body and soul were to him concurrent manifestations of the same essence.

Browne's scientific experience conditioned his philosophic imagination. In his synthesis of experience and reason he becomes a connoisseur of ideas. Like Hippocrates and Galen he maintains the unity in duality of matter and spirit. By induction from the data of science he arrives at a doctrine of the essence and relation of God, nature and man. The *Religio Medici* is his apologia for science, his defense against the charge of atheism as the great scandal of his profession.

But Browne was not only a scientist and philosopher but also an artist and a poet, and the creative impulse of his artistic imagination gave literary expression to his assimilation of science and philosophy. In Olympian attitude and perspective he was second only to Milton, and as a master of symphonic prose style he was unsurpassed. Even Shakespeare borrows phrases from him. And like Milton's, his imagery was even more auditory and musical than visual.

Anatomist, embryologist, philosopher, physician, poet, Browne was all these and, in the microcosm of his multitudinous nature, one of the greatest humanists of history, who fused science and art in the alembic of his genius by the fire of his philosophic imagination.

Change of Life: A modern woman's guide. By F. S. Edsall. 12°, cloth, 127 pp. New York: Woman's Press, 1949. $2.00.

This monograph on the menopause is an admirable popular presentation of the familiar phenomena of the climacteric. The author, though not a physician, writes with accuracy and authority, and shows thorough, scientific command of her field. Dr. Novak, in his foreword, points out that she "has included many subjects only indirectly related to the menopause, but which will interest the intelligent reader." After all, in both sexes, the problems of aging are far more psychologic than physiologic. The person who can adjust himself continuously and successfully to all the progressive changes of life is the one who not only will live most effectively and happily but also will meet most triumphantly the ultimate transition to eternity.

Surgical Management of Vascular Diseases. By Gerald H. Pratt. 8°, cloth, 496 pp., with 181 illustrations. Philadelphia: Lea and Febiger, 1949. $10.00.

In the last few years the work of many pioneers in peripheral vascular disease has come to fruition. There is now a considerable body of knowledge that enables the physician to treat disorders, many of which were considered entirely hopeless a decade or two ago. Attesting to this change in outlook is the appearance of several new works on the nature and treatment of peripheral vascular disease. Some of the happiest results are seemingly those following operative treatment of various types, and, since many surgeons now make a specialty of this sort of work, it is logical to find a volume like that of Dr. Pratt devoted to surgical indications and technics.

The author has given definite emphasis to his own technics in the treatment of peripheral vascular disease, which he covers quite fully. Diseases of vessels in other parts of the body, such as those of the thorax, the heart itself and the portal vein, are touched upon rather sketchily.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Synopsis of Hernia. By Alfred H. Iason, M.D., attending surgeon, Adelphi Hospital, director of surgery, Brooklyn Hospital for the Aged, and instructor in anatomy, New York Medical College. 8°, cloth, 500 pp., with 98 illustrations by Alfred Feinberg, instructor of medical illustration, Department of Pathology, Columbia University College of Physicians and Surgeons, New York City. New York: Grune and Stratton, 1949. $6.50.

This condensed work is intended for graduate and postgraduate students and for the practicing physician and surgeon. The text is divided into four parts: general considerations, in which are discussed the anatomy of the abdominal wall and the classification of hernias; external abdominal hernias; internal hernias; and rare and recurrent hernias. There is an appendix listing the eponymic names of hernias. There is a good index. The type and printing are good, but the use of a heavy-filled paper makes the small volume too heavy for its size.

Stomach Disease as Diagnosed by Gastroscopy. By Eddy D. Palmer, M.S., M.D., Major, Medical Corps, United States Army. 4°, cloth, 200 pp., with 109 illustrations. Philadelphia: Lea and Febiger, 1949. $8.50.

The text of this special monograph is divided into chapters on the various diseases afflicting the stomach. The first chapter discusses the normal stomach. There are also special chapters on the postoperative stomach, gastroscopy in diseases of the duodenum, liver and biliary tract, and in certain metabolic and skin diseases, and on gastroscopy and extrinsic tumors. The work is based on the author's experience at an Army hospital, and the literature of recent

years is discussed throughout the text. Bibliographies are appended to the individual chapters. There are indexes to the authors noted in the bibliographies and to subjects. The type, printing and illustrations are excellent. The book should be in all collections on diseases of the digestive tract.

Progress in Neurology and Psychiatry: An annual review. Vol. IV. Edited by E. A. Spiegel, M.D., professor and head, Department of Experimental Neurology, Temple University School of Medicine. 8°, cloth, 593 pp. New York: Grune and Stratton, 1949. $10.00.

This fourth volume of an important series is divided into four parts: the basic sciences, neurology, neurosurgery and psychiatry. The thirty-four reviews are the joint work of sixty-seven specialists in their particular fields. To each article is appended a select bibliography. The paper and type are good, and the volume is well published. There is a good index. The book is recommended for all medical libraries and should be available to all neurologists and psychiatrists.

Estudos Cirúrgicos. 5ª Série. By Eurico B. Ribeiro, Diretor do Sanatório São Lucas. 8°, cloth, 223 pp., with illustrations. São Paulo, Brazil: Editôra S. A. imprimiu, 1949.

This series contains twenty-nine papers of the author presented during 1944 and 1945. They cover all the aspects of operative surgery. The first article analyzes 10,000 operations performed during the period 1926 to 1942. There is an index for the complete series of five volumes.

Electrocardiographic Technique: A manual for physicians, nurses and technicians. By Kurt Schnitzer, R.T., M.D. 16°, cloth, 96 pp., with 46 illustrations. New York: Grune and Stratton, 1949. $3.50.

This manual is intended primarily for the technician without training in electrocardiography. The language has been kept as simple as possible, and no attempt has been made to include instructions concerning interpretation. The various electrocardiographic technics in general use in the United States are described. The text is concluded with a bibliography, and there is a good index. The small volume is well published. It should prove useful to interested persons.

Das Ekg-ABC: Eine Systematik zur Auswertung von Elektrokardiogrammen. By Max Waldhecker, Dr. med., Dr. rer. pol. 8°, paper, 114 pp., with 135 illustrations. Stuttgart: Georg Thieme, 1948. New York: imported by Grune and Stratton. $2.25.

This primer on electrocardiography is well done. The general part discusses briefly the heart conditions in which the method is used and the curves in general. In the special part the normal curve, types of curves, rhythm and frequency disturbances and the extrasystole, and the various curves from P through T are described. Illustrative curves are given for the various heart diseases. The depiction of the curves is excellent. There is a good index. The small book should be in all collections on the subject.

Diagnostische und therapeutische Eingriffe des Internisten: Vorbereitung, Technik, Komplikationen und Gefahren. By Dr. med. Eberhard Regenbogen, physician-in-chief, Medical Clinic of the Municipal Hospital, Osnabrück. 8°, cloth, 262 pp., with 28 illustrations. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $4.50.

This manual is concise but comprehensive in scope. It discusses the instruments and apparatus used in diagnosis and treatment. The text is divided into two parts, general and special. The general part considers among other topics asepsis and antisepsis, the care of apparatus and instruments, disinfection of the hand and operation field, the operation room and anesthesia. The special part covers the whole field of mechanical diagnostic procedures of all parts and organs of the body, including the eye, ear, throat and genitourinary tract. Under each topic are presented the instrument, technic, complications and dangers of the method. The book should prove useful for ready reference purposes.

Lehrbuch der Geburtshilfe. By Prof. Dr. med. Heinrich Martius, Director, Universitäts-Frauenklinik, Göttingen. With the assistance of Professor Dr. med. Werner Bickenbach and Professor Dr. med. Kurt Nordmeyer, with drawings by Käthe Droysen. First part: *Physiologie.* 4°, cloth, 568 pp., with 539 illustrations, partly colored. Second part: *Pathologie.* 4°, cloth, 605 pp., with 486 illustrations, partly colored. Stuttgart: Georg Thieme, 1948. $22.00. New York: imported by Grune and Stratton.

This standard reference work on obstetrics has been reprinted without alteration from the 1943 edition, making the treatise easily available to persons outside Germany. The treatise is divided into two parts, physiology and pathology. The pagination is continuous. The volumes are well published in a typical pre-war German style. The illustrations are excellent. The treatise should be in all special collections on obstetrics.

Medizinische Klinik, ein Fortbildungskurs für Ärzte. By Prof. Dr. Ferdinand Hoff, physician-in-chief; Medical Clinic of the Municipal Hospital, Aachen. 8°, cloth, 467 pp., with 74 illustrations. Stuttgart: Georg Thieme, 1948. New York: imported by Grune and Stratton. $9.00.

This clinical work, intended as a postgraduate course for physicians, covers the whole field of internal medicine. Thirty-five pages are devoted to the subject of diabetes. Case histories, totaling one hundred and nine, are interspersed throughout the text. There is an author-subject index and one of case histories.

Die Bazillenruhr. By Ludwig Roemheld. 8°, paper, 125 pp. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $3.25.

This monograph on bacillary dysentery, although concise, is comprehensive in scope. The pathogenesis, bacteriology, epidemiology and prevention inoculation, pathologic anatomy, diagnosis and treatment and prognosis are considered in different chapters. Case histories are interspersed in the text. The literature of the subject is well surveyed. A large bibliography concludes the book. The lack of an index is disappointing in an otherwise well published monograph.

Die Insulin-Lipodystrophie. By Prof. Dr. Ferdinand A. Kehrer, director of the Neuropsychiatric Clinic of the University of Münster, Westphalia. 8°, paper, 43 pp., with 9 illustrations. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $1.50.

This short monograph discusses a disorder of the subcutaneous fatty tissue occurring after the long use of insulin. The author describes a case in a forty-six-year-old woman with a family history of diabetes who had been using insulin for eighteen years. The pamphlet should be in diabetes collections.

Die Erkrankungen des Darmes. Appendix: *Die Prokto-Sigmoidoskopie.* By Walter Zweig (London), professor, University of Vienna. 8°, cloth, 253 pp. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $6.75.

This compact work on diseases of the intestinal tract is based on the author's experience of thirty years in the field of gastroenterology. It is devoted primarily to the diagnosis and treatment of the diseases commonly met with in everyday practice. The material is well arranged, and the text is well written. The book is divided into two parts: general and special. The first discusses briefly the anatomy and physiology, nutrition and metabolism of the intestines and the diagnostic procedures employed in their diseases. The second deals with acute and chronic enteritis, colitis, appendicitis, diarrhea and constipation, duodenal ulcer, cancer, enteroptosis, ileus and nervous diseases of the intestines. Proctosigmoidoscopy is dealt with in an appendix, in which the instrument and its use and the various diseases of the rectum and anus are discussed. The manual should prove useful to German-reading physicians. The publishing is surprisingly excellent and is well up to pre-war German standards. All the books and pamphlets issued by the well known publishing firm of Georg Thieme, noted herewith, are well done, and the publisher is commended for his outstanding accomplishment.

Darmbrand: Enteritis Necroticans. By K. Hansen and others from the Municipal Hospital, Lübeck. 8°, cloth, 212 pp., with 103 illustrations, some colored. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $7.50.

This monograph on necrotic enteritis is the joint work of six physicians of the Municipal Hospital of Lübeck. The etiology and pathogenesis, pathological anatomy, symptoms and diagnosis, surgical treatment, recurrence and complications, and the disease in children are discussed in separate chapters. The material is well arranged and well written. Case histories are interspersed throughout the text. A bibliography of German references concludes the volume. A detailed table of contents takes the place of an index. The book should be in all large medical libraries and in collections on gastroenterology.

Naegeli Differentialdiagnose der inneren Medizin. Third, unchanged edition. Published by Naegeli's students. 8°, cloth, 794 pp., with 190 illustrations, partly colored. Stuttgart: Georg Thieme, 1948. New York: imported by Grune and Stratton. $9.00.

This standard work, although designated the third edition, has been reprinted without alteration from the second war edition of 1942. The material is well arranged and covers the whole field of internal medicine as generally known, and also includes diseases of the joints and of the nervous system. The book is well published and should prove valuable to German-reading physicians.

Einführung in die innere Medizin. By Dr. Hans J. Wolf, professor extraordinary of internal medicine, University of Göttingen, and chief of the Internal Division, Municipal Hospital, in Bielefeld. Third enlarged edition. 8°, cloth, 608 pp., with 73 illustrations, partly colored. Stuttgart: Georg Thieme, 1948. New York: imported by Grune and Stratton. $7.25.

The first edition of this introduction to medicine was published in 1942. The present edition has been enlarged, especially on the subject of electrocardiography, which has been completely revised. The material is well arranged, and well published. There is a good index. The book should prove useful to German physicians.

Die elektrochirurgische Behandlung der Tuberkulose. By Heinrich Brügger. 8°, paper, 76 pp., with 99 illustrations, partly colored. Stuttgart: Georg Thieme, 1949. New York: imported by Grune and Stratton. $3.25.

This small monograph considers the use of diathermy in the treatment of cold abscesses in general, tuberculosis of the lymph nodes, fistulas in tuberculosis of the bones and joints and other fistulas. Numerous cases are cited throughout the text. The illustrations are excellent.

Marihuana in Latin America: The threat it constitutes. By Pablo O. Wolff, M.D., Ph.D., M.A., Buenos Aires, Argentina, member, Expert Committee on Habit Forming Drugs, World Health Organization. Sponsored by Washington Institute of Medicine. 8°, paper, 56 pp. Washington, D.C.; Linacre Press, Incorporated, 1949. $1.50.

This small pamphlet considers the subject of marihuana addiction in its various aspects, with particular emphasis on delinquency, criminality and its psychopathic manifestations. The situation in Mexico and the South American countries is discussed. A bibliography concludes the text. A table of contents serves as an index. The use of chapter headings instead of numerals would have added to the usefulness of the pamphlet.

NOTICES

94TH INFANTRY DIVISION LECTURES

The tenth lecture in the series sponsored by the 94th (Bay State) Division will be held in the amphitheater of the Evans Memorial, Massachusetts Memorial Hospitals, Harrison Avenue, Boston, on Wednesday, January 25, at 8 p.m.

Dr. L. Robert Weiss will speak on the subject "Recent Advances in Allergy."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will be shown during this period.

DEBATE ON COMPULSORY HEALTH INSURANCE

Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society, and Dr. Channing Frothingham, past president of the Society and a member of the American Medical Association, the American Society of Clinical Investigation and the Association of American Physicians, will debate at the Ford Hall Forum on Sunday, January 29, at 8:00 p.m.

The subject will be "Why Should Organized Medicine Oppose Compulsory Health Insurance?" (as provided for in Senate Bill 1679, title 7).

The Ford Hall Forum, Inc., is held in Jordan Hall, 30 Gainsboro Street, Boston. The doors will be open at 7:30. There is no charge for admission; to help meet expenses a collection is taken at the door.

AMERICAN BOARD OF OPHTHALMOLOGY

Candidates for the certificate of the American Board of Ophthalmology are accepted for examination on the evidence of a written qualifying test. These tests are held annually in various parts of the United States. Applications are now being accepted for the 1951 written test and will be considered in order of receipt until the quota is filled.

Practical examinations for acceptable candidates in 1950 will be held in Boston from May 22 to 26 and in Chicago from October 2 to 6 and in January, 1951, on the West Coast.

A new directory of all diplomates to date, arranged alphabetically and geographically, will be published early in 1950. No biographic material will be included.

Diplomates are urged to keep the Board office informed of all changes of address.

ATOMIC ENERGY COMMISSION RESEARCH FELLOWSHIPS

The National Research Council has announced a modified program of postdoctoral research fellowships in the medical sciences, supported by the Atomic Energy Commission. It is the purpose of these fellowships to train a limited number of men and women for research in aspects of the medical sciences whose development is the direct responsibility of the Atomic Energy Commission, including studies of the physiologic and toxicologic effects of fission products. These investigations require at some stage the use of special facilities available in AEC installations and the development of radiation instruments for use in the study of problems of a classified nature in the field of the medical sciences. Because these fellowships are for training in fields where some or all information is classified, the applicant's loyalty to the Government must be determined by a check by the Federal Bureau of Investigation of the character, association and loyalty of the applicant before payment of the fellowship stipend is approved.

A Fellow must be a citizen of the United States under thirty-five years of age at the time of appointment, with training in some branch of the biologic or medical sciences equivalent to that represented by the M.D. or Ph.D. degree, and must present promise of research ability. Holders of the M.D. degree must have completed one year of internship or work that, in the opinion of the Fellowship Board, is equivalent.

Applications must be completed by February 15, 1950. Appointments will be for one year unless a shorter term is approved by the Fellowship Board, and must terminate on or before June 30, 1951.

Requests for additional information and application blanks should be addressed to the AEC Postdoctoral Fellowship Board in the Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

(*Notices concluded on page xiii*)